The economic analysis of visceral leishmaniasis control

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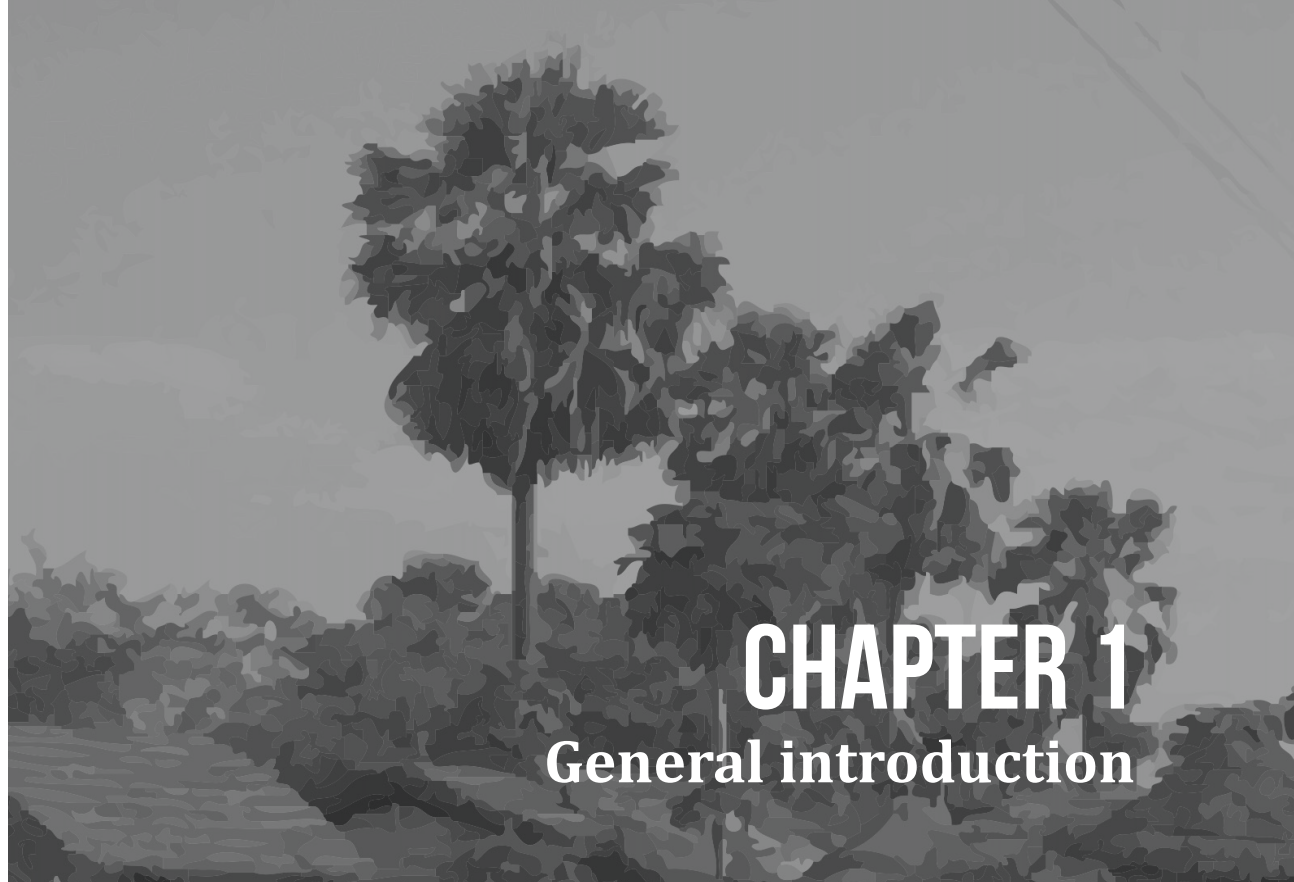

CHAPTER 1
General introduction

This introduction is based in part on:

- Meheus F, Boelaert M (2010) The burden of visceral leishmaniasis in South Asia. Trop Med Int Health 15: 1-3.
- Meheus F, Rijal S, Lutumba P, Hendrickx D, Boelaert M (2012) NTD control and health system strengthening. Lancet 379: 2149-50 [letter].
- Uranw S, Hasker E, Roy L, Meheus F, Das ML, Bhattarai NR, et al. (2013) An outbreak investigation of visceral leishmaniasis among residents of Dharan town, eastern Nepal: evidence for urban transmission of L. donovani. BMC Infect Dis 13:21.
- Lutumba P, Makieya E, Shaw A, Meheus F, Boelaert M (2007) Human African trypanosomiasis in a rural community, Democratic Republic of Congo. Emerg Infect Dis 13: 248-254.

INTRODUCTION

Visceral leishmaniasis (VL) is a vector-borne disease caused by *Leishmania* parasites that are transmitted by the bite of an infected female sandfly. VL is an important public health problem and a significant cause of mortality and morbidity in the Indian subcontinent and East Africa. Since 2005 the governments of India, Nepal and Bangladesh are engaged in a collaborative effort to control and eliminate visceral leishmaniasis from the Indian subcontinent. Approaches to control aim on the one hand at improving the human recovery rate through early diagnosis and case management and on the other hand reducing vector density and biting rate through vector control interventions such as indoor residual spraying (IRS) and the use of bednets (WHO 2005). In East Africa such an integrated effort to control VL does not yet exist and control is mainly based on passive case detection and treatment, although bednets are distributed by non-governmental organizations (Ritmeijer *et al*. 2007).

However uptake of VL interventions remains low. VL occurs in regions with weak health systems and low quality public health services. The costs associated with an episode of VL are substantial and may drive already impoverished households further into poverty (Meheus *et al.* 2006; Uranw *et al.* 2013). In addition long delays in diagnosis are common since clinical symptoms often resemble that of other infections and households usually first visit informal or private health providers where health workers lack knowledge about appropriate treatments, and do not have the tools to diagnose VL. As a result VL affected households incur substantial financial and economics costs in seeking appropriate care.

Over the past years various new technologies have become available that may improve VL case management. Newer drugs provide opportunities for shorter, less expensive treatments that can be provided on an ambulatory basis, including the first oral VL drug, Miltefosine, adopted by the VL elimination initiative as first line treatment, and paromomycin which is very cheap (US$15 for an adult full course) and administered intramuscularly. However both drugs are vulnerable for development of parasite resistance (Bryceson 2001; Seifert *et al.* 2003). More recently, a short course of liposomal amphotericin B showed to be very efficacious (Sundar *et al.* 2010), although the cost of the drug is still a barrier for use as a first line. Combination therapy for the treatment of visceral leishmaniasis has increasingly been advocated as a way to increase treatment efficacy and tolerance, reduce treatment duration and cost, and limit the emergence of drug resistance (Alvar *et al.* 2006; Croft *et al.* 2006). Once definite results from clinical trials are available combination therapies can be considered as first line treatment. The development of the rK39 immunochromatographic test, a rapid diagnostic test with high sensitivity and specificity, and the Direct Agglutination Test (DAT) make the rapid diagnosis

of VL possible and are less invasive than previous procedures (Sundar *et al.* 2002b). As these several options became available, the debate surrounding the best policy for case detection and treatment flared up.

Economic analysis provides an important set of tools to underpin the choice for evidence-based policy. Given the limited financial resources available to VL control and the increasing number of possible interventions, especially regarding drug treatment, economic evaluation provides us with methods to systematically compare all relevant options in terms of their costs and consequences and thereby contribute to more rational decision-making and efficient allocation of scarce resources. Moreover it can improve our understanding of factors influencing both the supply of VL interventions and factors related to the behaviour of VL affected households. While economic analysis is increasingly recognized by both national and international policy makers as an important tool in the development of VL control policies, the scarcity of reliable data, in particular on costs, severely hampers efforts to control the disease.

Against this background, I focus in this thesis on different aspects of economic analysis for VL control. The studies were carried out in three VL endemic countries – Nepal, India and Sudan. In the following paragraphs an overview is provided on the epidemiological and public health aspects of VL followed by the objectives and outline of the thesis.

LEISHMANIASIS

There are about twenty different species of leishmania that cause disease in humans. They cause a spectrum of diseases broadly categorized as cutaneous, mucocutaneous (MCL) and visceral leishmaniasis. Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis and is endemic in 82 countries across all continents except Australia. The disease causes ulcers or nodules on exposed parts of the body (face, arms or legs) where the sand fly has bitten. CL is an important cause of disability, stigma and social isolation especially among women (Reithinger *et al.* 2005). MCL is a severe form of CL with progressive destructive ulcerations developing at the mucosal regions of nose and mouth and spreading to the throat (Chappuis *et al.* 2007). MCL is highly disfiguring and primarily occurs in Brazil, Bolivia & Peru.

The most severe form of leishmaniasis is visceral leishmaniasis (VL) and is fatal if untreated. VL is often referred to as *kala-azar*, which means black fever in Hindi due to the hyperpigmentation of the skin that may occur during the course of the disease (Sanyal 1985; Pearson & de Queiroz Sousa 1996). VL is mainly caused by the parasite species *L. donovani* (Chappuis *et al.* 2007) and transmitted by the bite of an infected female sandfly from infected to uninfected humans (i.e. anthroponotic VL; AVL). Although in East Africa, the presence of parasites has been shown in

rodents (Elnaiem et al. 2001) and dogs (Dereure et al. 2003), it is unclear whether there is also zoonotic transmission (i.e. from animals to humans) (Elnaiem *et al.* 1998a). On rare occasions VL transmission by blood transfusion has also been documented (Singh *et al.* 1996; Dey & Singh 2006).

Clinical signs and symptoms of VL include prolonged fever, fatigue, weakness, loss of appetite, weight loss and enlargement of the spleen and liver. After several months, untreated VL will result in the death of the infected individual mainly due to cachexia, bleeding and/or from secondary infections (Berman 1988). About 5-10% and 50% of patients that recover from VL after treatment in the Indian subcontinent and East Africa respectively, develop a skin condition named post kala-azar dermal leishmaniasis (PKDL) (Zijlstra 2001; Zijlstra *et al.* 2003). Depending on the grade of severity, PKDL develops as a rash, usually around the mouth and spreading to other parts of the body such as the arms and the upper torso (Zijlstra *et al.* 2003). Because parasites can be found within the lesions, PKDL is considered an important reservoir for the human transmission of the disease between epidemic cycles (Addy & Nandy 1992).

BURDEN OF VL: INCIDENCE AND MORTALITY

VL is reported in 62 countries (figure 2) with 200 million people at risk (Desjeux 1996). Recently the WHO estimated that worldwide about 200,000 to 400,000 new cases of VL and 50,000 to 60,000 deaths occur annually with the majority of VL cases (>90%) concentrated in only four countries: Bangladesh, India, Brazil and Sudan (WHO 2010; Alvar *et al*. 2012).

However because of a lack of reliable empirical data there is much uncertainty on figures of VL incidence. In the Indian subcontinent, the current officially reported figures are obtained through passive case detection in government health services and usually do not include cases detected by the private for-profit sector, which constitute a majority of the VL care providers in India. These figures therefore largely underestimate the actual number of cases. Extrapolation from official data sources is also difficult due to the focal distribution of VL (Bern *et al.* 2008). A number of studies have estimated the degree of underreporting, although these studies were limited to specific geographical areas. For instance, Desjeux (1992) found a 1:5 ratio of reported to unreported VL cases in community surveys in India. Singh *et al.* (2006) documented underreporting by a factor of eight in a community development block in Muzaffarpur district in Bihar, India in 2001–2003 and more recently Singh *et al.* (2010) estimated underreporting by a factor of four in Vaishali district, also in Bihar. In south Sudan, Collins *et al.* (2006) estimated that 91% of VL deaths were undetected.

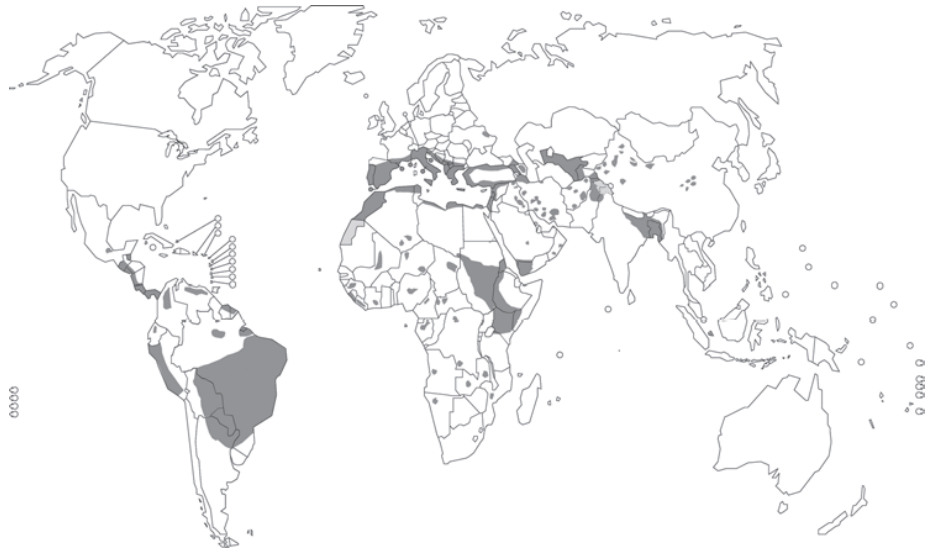

Figure 1: Geographical distribution of visceral leishmaniasis
Source: WHO 2010

The annual reported and estimated number of VL cases in the three study countries are shown in table 1. In Nepal, VL is reported in 12 districts situated in south-eastern Nepal in the Terai region bordering the highly VL-endemic northern state of Bihar in India. More than 90% of all cases in India are reported from Bihar State. In Sudan, Gedaref State is the epicentre of VL in East Africa (Burki 2009). The region is prone to epidemics and frequent outbreaks of VL with high case-fatality rates caused among other by malnutrition as well as mass population displacements due to war and famine. Between 1984 and 1994, a major epidemic of VL resulted in an estimated 100,000 VL deaths in the Western Upper Nile province of Sudan (Seaman *et al.* 1996). In 2010, Médecins sans Frontières reported an outbreak of VL in South Sudan leading to an eight-fold increase in the number of treated patients compared to the previous year (Médecins sans Frontières 2010).

Table 1: Reported and estimated annual incidence of visceral leishmaniasis in India, Nepal and Sudan

	Reported VL cases/year	Estimated annual VL incidence		
India	34,918*	146,700	to	282,300
Nepal	1,477*	3,000	to	5,900
Subtotal Indian subcontinent and South East Asia	42,623	162,100	to	313,600
Sudan	3742*	15,700	to	30,300
Subtotal East African region	8,569	29,400	to	56,700
Elsewhere	7,034	6,200	to	18,800
Total worldwide	58,227	202,200	to	389,100

* Years of report: Sudan 2005-2009; India & Nepal: 2004-2008
Source: Compiled from Alvar *et al.* 2012

ECONOMIC BURDEN OF VL

The economic burden of VL is measured in terms of two broad categories of costs. These include the direct costs associated with accessing treatment (e.g. drugs, laboratory tests, transportation) and the indirect costs associated with for example absenteeism or reduced productivity due to VL illness, which translates into an income loss to the household. For a review on the economic burden of VL we refer to chapter 2.

CONTROL OF VL

In the absence of a vaccine and in areas with *L. Donovani* transmission, the control of VL is mainly based on accurate diagnosis and treatment, combined with vector control (Boelaert *et al.* 2000).

Vector control

Indoor residual spraying (IRS) is the most widely used intervention and is implemented routinely in India and Nepal by spraying houses twice yearly in villages where a case of VL had been reported in the year before. IRS has been shown to be effective in reducing sandfly density in India and Nepal where the sandfly (*Phlebotomus argentipes)* is endophilic and rests inside cracks and crevices of mud plastered walls (Kaul *et al.* 1994; Kumar *et al.* 2009; Das *et al.* 2008). Although there are no studies that looked at the effects of IRS on VL transmission and incidence, the large scale spraying campaigns organized in the 1950s in an effort to eradicate malaria also reduced kala-azar incidence in the region (Birley *et al.* 1993). VL subsequently re-emerged in the early eighties with the discontinuation of the spraying activities (Bern & Chowdhury 2006). In Sudan, and eastern Africa, the sandfly species is different (*Phlebotomus orientalis*) and transmission occurs both in villages (Hassan et al. 2004; Elnaiem & Osman 1998) and outside in *Acacia/Balanites* forests (Elnaiem *et al.* 1998b; Thomson *et al.* 1999). Because individuals are exposed differently to sandflies, e.g. by sleeping outside during the dry season (Ritmeijer et al. 2007) or through activities such as shepherding (Hoogstraal & Heyneman 1969; Chappuis *et al.* 2007) IRS is thought to be less efficacious and no spraying activities are currently taking place. Insecticide treated nets (ITN) have been distributed in Sudan by Médecins sans Frontières. While ITNs are also distributed in India and Nepal, the evidence on the effectiveness of insecticide treated nets (ITN) is mixed. Although some studies showed sleeping under a bednet to be a protective factor against VL (e.g. Bern *et al*. 2000; Bern *et al.* 2005), recent evidence from a community intervention trial of LLIN in the Indian subcontinent suggests a 25% reduction in vector density but not leading to reduced VL incidence compared to control areas where untreated bednet use was high (Picado *et al.* 2010).

Case detection and management

Diagnosis

The clinical diagnosis of VL is difficult because the signs and symptoms are not characteristic to VL only and may be confused with other diseases such as malaria, schistosomiasis or typhoid fever (Singh 2006). Microscopic confirmation of parasites in aspirates of lymph nodes, bone marrow or spleen is the recommended method of diagnosis for VL (Chappuis *et al.* 2007; WHO 2010). However, the sensitivity of microscopic examination varies. Splenic aspiration has the highest sensitivity, but is an invasive and complex technique and life-threatening bleeding can occur (Boelaert *et al.* 2007). The rK39 immunochromatographic test (rK39) and the Direct Agglutination Test (DAT) have now largely replaced these tests (Sundar *et al.* 2002b). Both the rK39 and DAT are recommended by the VL elimination initiative in India and Nepal (WHO 2005) and national guidelines in Sudan. However, the rK39 seems to be less sensitive in Sudan compared to India and Nepal (Ritmeijer *et al.* 2006) and in case of a negative test result, a second test is still required.

Treatment strategies

Treatment options for VL are limited and treatment policies vary across countries and regions. There are currently five drugs available for the treatment of VL. Pentavalent antimonials (sodium stibogluconate and meglumine antimoniate) have been the first line treatment for VL for over 70 years. They exist in both branded (Pentostam®, Glucantime®) and generic forms (produced by Albert David Ltd. in India). Generic antimonials are as effective as their branded counterparts but are up to 4 times cheaper (Veeken *et al.* 2000; Moore *et al.* 2001; Ritmeijer *et al.* 2001). The recommended treatment schedule for antimonials is 20 mg/kg/day for 20

to 30 days and is usually administered intramuscularly on a daily basis. Antimonials are toxic drugs with frequent adverse side effects such as cardio-, hepato- and nephrotoxicity (Ballou *et al.* 1987). In eastern Africa, antimonials are still the first line treatment for VL and patients are usually admitted for the full duration of treatment to monitor side effects and ensure adherence. In India and Nepal, antimonials are no longer recommended due to increasing reports of treatment failure (Lira *et al.* 1999; Rijal *et al.* 2003; Sundar 2001; Croft *et al.* 2006). Nonetheless a recent study showed they continued to be used in peripheral health facilities in Bihar (Hasker *et al.* 2010).

Conventional amphotericin B deoxycholate has still very high cure rates in the Indian subcontinent and is now most often used as second-line treatment (Sundar *et al.* 2004; Thakur *et al.* 1999). The drug is administered intravenously with 15–20 slow infusions of 1 mg/kg given either on a daily or alternate basis (Sundar et al. 2004). Amphotericin B shares drawbacks with antimonials such as the length of therapy (28-30 days) and parental administration. Because of its potential toxicity and mode of administration, hospitalization is required for the full duration of treatment (Murray 2000).

Three other drugs have been approved for the treatment of VL, but the efficacy and required dosage have been shown to differ between the Indian subcontinent and East Africa (WHO 2010). Lipsosomal Amphotericin B (Ambisome; Gilead), a lipid formulation of amphotericin B, is considered the best monotherapy for anthroponotic VL (WHO 2010). A single dose of liposomal amphotericin B delivered intravenously, was shown to be very effective in the Indian subcontinent and resulted in less side-effects compared to other anti-leishmanial treatments (Sundar *et al.* 2010; Thakur 2001). The very high price has prevented its widespread use as first line treatment but preferential pricing agreements negotiated by the WHO (Matlashewski *et al.* 2011) and a recent donation of 445,000 vials to treat 50,000 patients in the coming 5 years may change this (WHO 2011). Miltefosine is the first oral drug for VL and was originally developed as an anti-cancer drug. The drug is administered orally for 28 days, but is possibly teratogenic and cannot be administered to pregnant women or women in childbearing age that refuse the use of contraceptives (Sundar *et al.* 2002a). Despite these limitations, it was adopted as first line treatment by the VL elimination initiative in the Indian subcontinent. Aminosidine (paromomycin), an antibiotic with good anti-leishmanial activity has been registered in India since 2006. It is administered intramuscularly for 21 days, has few side effects and is very cheap. At a dosage of 15mg per kg per day it has been shown to be effective in India (Sundar *et al.* 2007), but not in East Africa in a phase II trial (Musa *et al.* 2010). Both miltefosine and paromomycin have a long half-life and are suspected to rapidly generate resistance (Sundar & Murray 2005; Perez-Victoria *et al.* 2006; Seifert *et al.* 2007). An overview of the current

monotherapies, their clinical efficacy, toxicity and disadvantages are presented in table 1 of Chapter 7.

As there are no new compounds for VL expected to come to the market in the near future, combination therapy, as used successfully against malaria and tuberculosis, is increasingly being considered as a possibility to delay or prevent the emergence of resistance to the currently available VL drugs. Combination therapies may also increase tolerability, reduce treatment duration and possibly (direct and indirect) costs. Médecins sans Frontières in southern Sudan already used a combination of sodium stibogluconate with paromomycin during an epidemic (Ritmeijer and Davidson 2003). For a complete overview and discussion of combination therapies we refer to Chapter 7.

VL: A NEGLECTED DISEASE

The World Health Organization (WHO) considers VL as a neglected tropical disease (NTD). The NTDs are a group of chronic vector-borne protozoan, helminthic and bacterial infections including VL and other diseases such as hookworm infections, schistosomiasis, lymphatic filariasis, African trypanosomiasis, buruli ulcer or leprosy (WHO 2012). These diseases affect almost exclusively poor rural populations and are considered "neglected" as they are under-researched and lack adequate funding for their control, although recently a number of diseases have been given higher priority by the international donor community. Together, the NTDs affect more than a billion people worldwide and cause the loss of 57 million disability adjusted life-years (DALYs), a burden higher than tuberculosis or malaria (Hotez *et al.* 2006b). They are an important cause of disability (e.g. lymphatic filariasis), disfigurement and stigma (e.g. cutaneous leishmaniasis) (Beyrer et al. 2007; Perera et al. 2007), blindness (onchocerciasis) (Boatin & Richard 2006), anaemia and malnutrition (e.g. schistosomiasis, hookworm infections) (King *et al.* 2005) and death in developing countries (e.g. schistosomiasis, ascariasis, visceral leishmaniasis) (Hotez *et al.* 2006a; Alvar *et al.* 2012). A common feature of the NTDs is their inextricable link with poverty. On the one hand NTDs often cluster in the same geographical areas, primarily in low-income countries, where the poor and disadvantaged are most at risk of infection with one or more NTDs due to poor living and working conditions, inadequate sanitation or lack of access to safe drinking water and health care. On the other hand, the NTDs are also an important determinant of poverty through their effect on child development, the reduced productivity of infected individuals and the costs related to accessing treatment services. For example children infected with schistosomiasis or hookworms are more absent from school, perform less well and have diminished cognitive abilities (De Clercq *et al.* 1998; Sakti *et al.* 1999; Jukes *et al.* 2002), which may impact their educational achievements and lead to

lower wage-earning potentials in the future (Hotez *et al.* 2009). The physical impairments, such as the swelling of the legs caused by lymphatic filariasis (i.e. elephantiasis), prevents infected individuals from working in the fields or performing other productive activities (Ramaiah et al. 2000; Gyapong et al. 2000) which has a negative impact on the income of the household. The stigma caused by diseases such as lymphatic filariasis, or the disfigurement from lesions to the face and visible parts of the body in the case of cutaneous leishmaniasis often leads to physical and emotional isolation (Reitinger *et al.* 2005) or even exclusion from community life (Wiess 2008). Other NTDs, like visceral leishmaniasis, have a direct effect on household wealth through catastrophic health expenditures on treatment and sales of livestock or assets to pay for the costs of care (Adhikary *et al.* 2009; Sharma *et al.* 2006; Meheus *et al.* 2006).

OBJECTIVES AND OUTLINE OF THE THESIS

Objectives

Visceral leishmaniasis disproportionally affects the poorest population groups in low-income countries. For the control, or even elimination, of VL to be successful, it will require a great deal of effort that needs to be sustained over the longer term. Ultimately, effective control of VL will depend on a mix of interventions, consisting of early and efficient diagnosis and treatment, with drug regimens that put as little burden as possible on both the patient and the health system. However, the scarcity of reliable data, both epidemiological and economic, contributes to the low visibility and priority given to VL by national control programmes and international donors.

The general objective of this thesis was to improve our understanding on the economic aspects of visceral leishmaniasis, provide evidence for more rational decision making on diagnosis, case management and VL control and justify increased investment in VL research and control in the Indian subcontinent and East Africa.

More specifically, the studies included in this thesis were framed around the following specific objectives (figure 2):

a. To understand the burden of visceral leishmaniasis in India, Nepal and Sudan;
b. To provide a better understanding of the health seeking behaviour and costs of VL illness from the provider and household perspective;
c. To examine the cost and cost-effectiveness of VL treatment alternatives with a focus on combination therapies.

The studies were carried out in collaboration with research partners in the three countries, in particular the BP Koirala Institute of Health Sciences (Dharan, Nepal), the Institute of Medical Sciences, Banaras Hindu University (Varanasi, India) and the Institute of Endemic Diseases, University of Khartoum (Khartoum, Sudan). International partners involved in the studies include the Drugs for Neglected Diseases Initiative and the World Health Organization (Geneva, Switzerland).

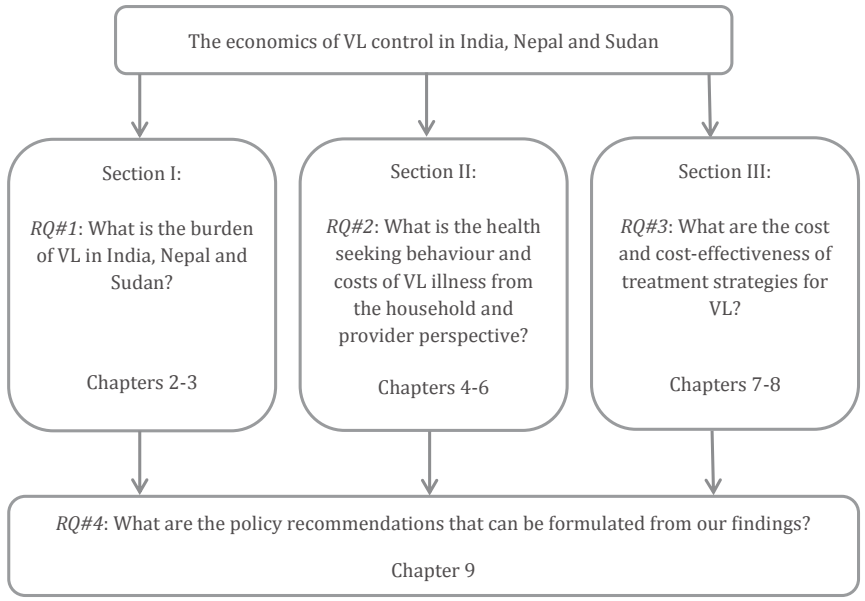

Figure 2: Overview of the thesis by research questions (RQ)

Outline of the thesis

The thesis is divided into three sections structured around the specific objectives described above that examine different aspects in the field of health economics applied to VL. In the first section on the burden of VL we present two studies. *Chapter 2* provides an overview of studies that investigated the socio-economic aspects of two neglected tropical diseases: visceral leishmaniasis and sleeping sickness. Both of these diseases affect the poorest of the poor in endemic countries, cause considerable direct and indirect costs (even though the national control programmes tend to provide free care) and push affected households deeper into poverty. In *chapter 3* we compared the socio-economic profile of households in areas with high VL endemicity to the

general population in Bihar State in India. The aim was to assess whether VL truly affects the poorest of the poor, a statement that is often made but had never been substantiated before. The data for this comparison were obtained from a community intervention trial in VL-endemic areas and the National Family Health Survey of India. In the second section of the thesis we estimated the cost-of-illness of VL In India, Nepal and Sudan. In India (*chapter 4*) we examined the economic costs (direct and indirect) of VL treatment from the societal and household perspective at a charitable hospital in Bihar, India. At the time, it was the first economic study on VL to be conducted in India. In Nepal (*chapter 5*) we carried out a household survey in 5 districts in Nepal to assess the economic impact of VL on households and examine whether the intensified VL control efforts induced by the VL elimination initiative resulted in a decrease in household costs. It was the largest study of its kind in Nepal to systematically estimate the cost incurred by households at all health providers, both public and private, when seeking VL care. In Sudan (*chapter 6*) we estimated the cost of providing VL diagnosis and treatment services (i.e. health-care provider perspective) and the cost to patients and their family to access these services (i.e. household perspective) at three health care facilities in Gedaref State. Besides costs, these studies also examined health seeking behaviour, strategies to cope with the costs of illness and the extent of catastrophic health expenditures households incurred. In the third and last section of the thesis we carried out a review on the current evidence and potential of combination therapies (*chapter 7*), while in *chapter 8* we analysed the cost and cost-effectiveness of treatment strategies for VL in the Indian subcontinent with a focus on combination therapies. The final *chapter 9* discusses our findings.

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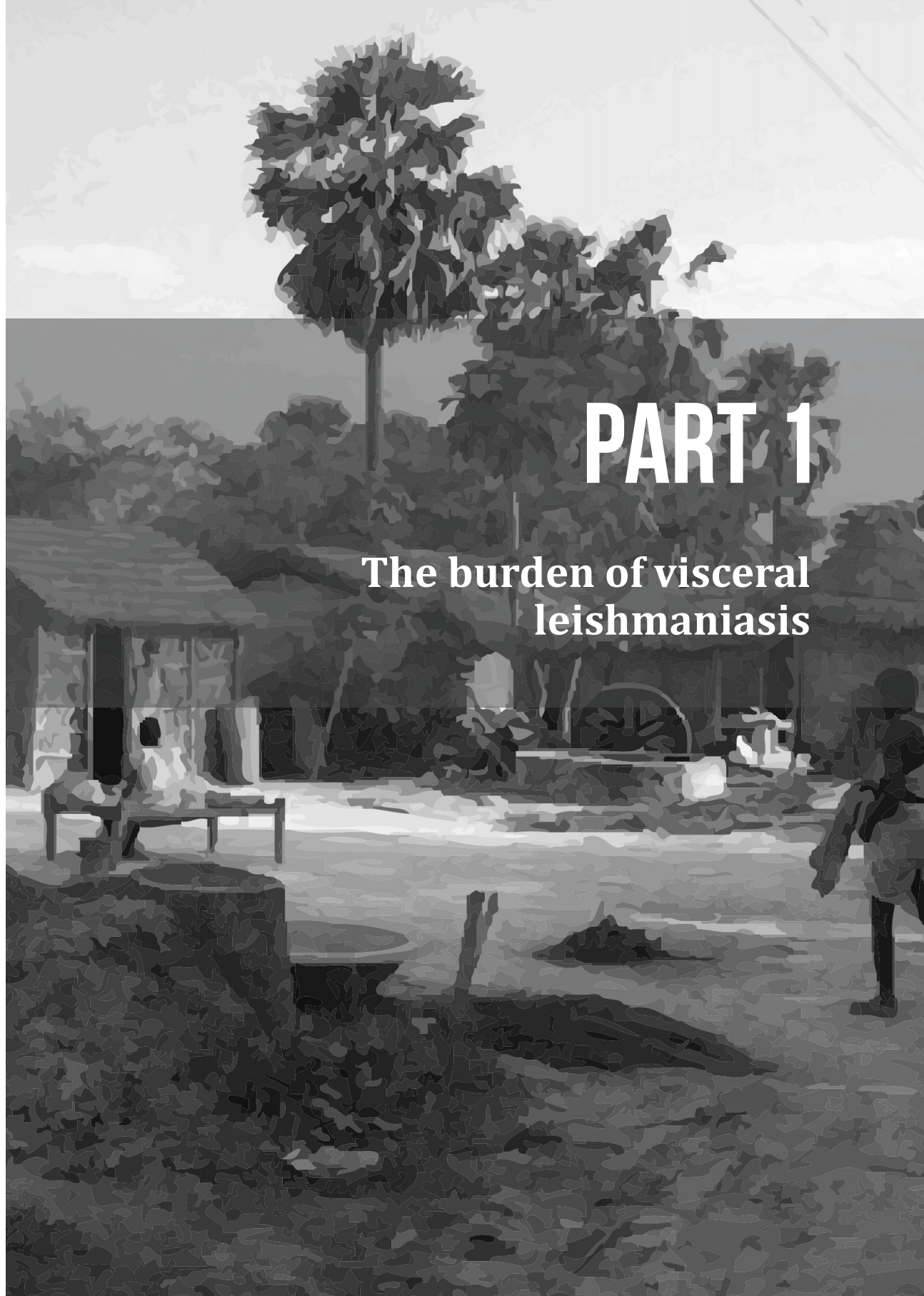
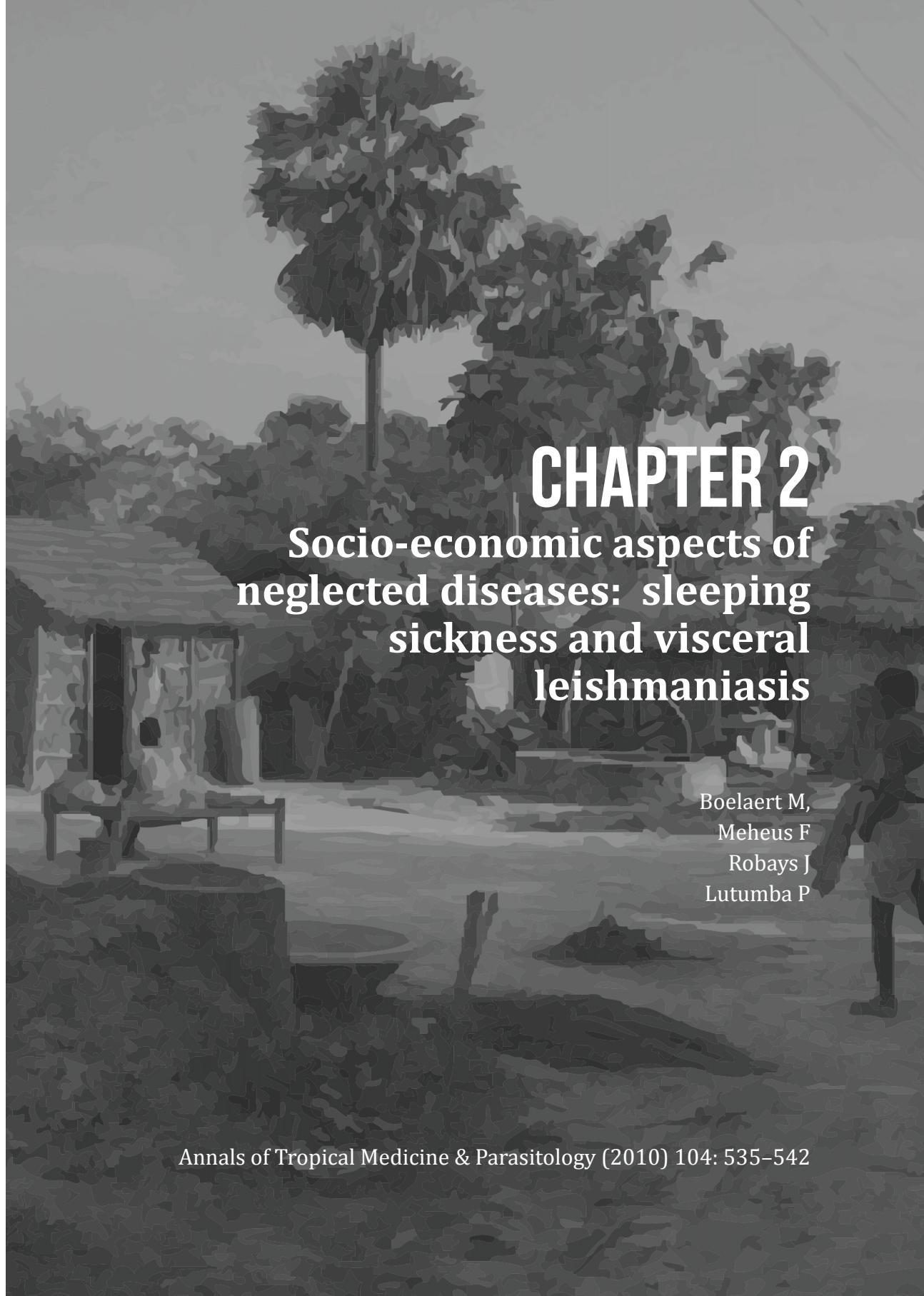


PART 1

The burden of visceral leishmaniasis



CHAPTER 2

Socio-economic aspects of neglected diseases: sleeping sickness and visceral leishmaniasis

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ABSTRACT

Several tropical diseases that are essentially poverty-related have recently gained more attention under the label of 'neglected tropical diseases' or NTD. It is estimated that over 1000 million people currently suffer from one or more NTD. Here, the socio–economic aspects of two NTD— human African trypanosomiasis and human visceral leishmaniasis — are reviewed. Both of these diseases affect the poorest of the poor in endemic countries, cause considerable direct and indirect costs (even though the national control programmes tend to provide free care) and push affected households deeper into poverty.

The neglected tropical diseases of humans (NTD) include a wide range of mainly, but not exclusively, parasitic diseases that can be usefully considered as a group because they are concentrated almost entirely among the poorest populations in the least-developed countries. Recent advocacy campaigns led the international donor community to give higher priority to these neglected health issues that, taken together, contribute a substantial part of the burden of disease in the tropics (Holveck *et al.* 2007). As NTD are so strongly related to poverty, an understanding of the socio–economic context is essential for their control. The available information on the socio–economic aspects of sleeping sickness and visceral leishmaniasis, two vector-borne diseases that are intrinsically poverty-related, is reviewed below.

SLEEPING SICKNESS

In the fields of research and control, sleeping sickness or human African trypanosomiasis (HAT) is a typical example of a 'neglected disease' (Trouiller *et al.* 2001, 2002). The numerous scientific articles on the unique immunological properties of trypanosomes contrast with the few papers that have been published on improvements in the diagnosis, treatment and control of HAT.

The large HAT outbreaks observed in colonial times have been attributed to forced displacement and deterioration in living conditions (Welburn *et al.* 2004). As HAT posed a threat to the economic development of large areas, the colonial authorities did invest in research on the diseases and the development of control tools. Large campaigns for the (mandatory) screening of populations were set up, and by the 1960s the disease had almost disappeared from Central Africa. Control methods have not fundamentally changed since this colonial period, although screening is no longer mandatory. The 1990s brought the progressive introduction of a serological test for mass screening —the card agglutination test for trypanosomiasis (CATT; Magnus *et al.* 1978) — and, more recently, eflornithine (Nightingale 1991) or a nifurtimox–eflornithine combination have been proposed, as alternatives to melarsoprol, for the treatment of stage-2 sleeping sickness (Priotto *et al.* 2009). The case-management strategy still remains complex, however, and much uncertainty surrounds the effectiveness of tsetse control.

The funding of HAT control currently depends nearly entirely on international aid. Interruptions in control efforts, linked to civil unrest in the affected areas, have led to spectacular re-emerging epidemics in recent years, in Sudan (Moore *et al.* 1999), Angola (Stanghellini & Josenando 2001) and the Democratic Republic of Congo (DRC; Lutumba *et al.* 2005). Although the global incidence of HAT seems to be declining, several non-governmental organizations (NGO) have warned that claims that HAT could be eliminated in the near future are probably premature,

given the 'hidden epidemic' in regions affected by civil war, in north–eastern DRC, southern Sudan and the Central African Republic (Chappuis *et al.* 2010).

The high burden that HAT places on affected households and communities is often not very visible in national or regional health data because of its focal nature. Within HAT foci, prevalence is often around 1% and, in the absence of control, it can rise relatively rapidly, sometimes to 50% in certain villages. Thus, much of the burden of this disease often falls, very heavily, on a few locations (Lutumba *et al.* 2007). The direct effects of sleeping sickness are mainly felt by economically active adults, and the cases require a great deal of intensive care, often from the other adults in their families. The seeking of a diagnosis and treatment are costly and time-consuming, and the economic burden on the household of an HAT case is high — between 1.5 and 10 months of household income, even when the diagnostics and anti-trypanosomal drugs are provided free of charge (Lutumba *et al.* 2007).

There have been few attempts to quantify the full costs borne by households with HAT cases, which include the costs of care at home and during hospital treatment, the costs of seeking a diagnosis, income lost by the HAT cases and their carers, medical fees, and the costs of transport. In the Republic of Congo, a case of HAT who was correctly diagnosed and treated was found to cost his or her household the equivalent of 2.6–5 months of household income from agriculture (Gouteux *et al.* 1987). In their more recent study in the DRC, where the direct costs of screening and treatment are fully subsidized by a national HAT programme, Lutumba *et al.* (2007) estimated the mean household costs for a diagnosed and treated case of HAT to be 5 months of household income, with such costs rising to over 10 months of household income for a case with complications. The costs of HAT treatment that are borne by households may be so high that they inhibit the timely uptake of treatment. When they discover that they have cases of HAT, households often take their time to prepare themselves financially and mobilize the necessary resources (often relying on the solidarity of the extended family), before the cases present themselves for treatment. High household costs (or, rather, the fear of being identified as an HAT case and then having to bear such expense) may partly explain the low levels of participation often seen at active-screening sessions organized by mobile teams (Robays *et al.* 2004).

There have been few published studies on the economics of controlling HAT, and fewer still on the comparative cost-effectiveness of vector control, at least in the context of dealing with HAT rather than trypanosomiasis in livestock. The costs of vector control to reduce the transmission of the parasites causing HAT have been estimated as U.S.$17,400/25,000 inhabitants over 3

years (Gouteux & Sinda 1990), U.S.$0.90/person-year (Lancien 1991), or 2000 CFA francs/person in year 1 and 250 CFA francs/person-year subsequently (Laveissière & Couret 1986). The costs of various approaches to active case-finding and treatment have been studied in several contexts and areas (Shaw & Cattand 2001), including the DRC (Lutumba *et al.* 2007). When Shaw (1989) compared the costs of vector control with the finding and treatment of human cases, she found active case-finding to be the more cost-effective option. The assumptions that Shaw (1989) made on the effectiveness of such case-finding were, however, probably optimistic compared with the trends observed in real-life settings (Robays *et al.* 2004).

VISCERAL LEISHMANIASIS

The World Health Organization estimates the incidence of human visceral leishmaniasis (VL) at 500,000 new cases/year (Murray & Lopez 1996[1]), with 90% of cases occurring in just four countries: India, Bangladesh, Brazil and Sudan (Desjeux 1996).

Desjeux (1996) characterised VL patients as '*those of lowest socio–economic status, who have minimal political power to influence the decisions of the government and a very limited capacity to assume the costs of the disease.*' At country level, leishmaniasis is often a hidden problem, as cases usually live in remote areas with poor access to services, and case loads are poorly documented, with five to eight unreported cases for every case that is reported (Singh *et al.* 2006, 2010b; Das *et al.* 2010). As VL, like HAT, often has a very focal distribution, the national (country aggregated) figures on VL incidence often fail to reflect the heavy burden on the worst affected communities. The 'hyper-clustering' of VL cases has recently been described in Nepal (Rijal *et al.* 2010) and India (Singh *et al.* 2010a), where the incidences in endemic clusters have been found to be 10 times higher than those reported at the corresponding district level.

In industrialized countries, the leishmaniasis of humans were not perceived as a direct threat until their emergence as a co-infection in HIV/AIDS, and, since the number of cases seen annually in the Mediterranean region has declined (as the result of widespread use of highly active antiretroviral therapy), such diseases seem to have disappeared again from the local public-health agenda (Dujardin *et al.* 2008).

The importance of VL as a hindrance to economic development is still not fully recognised although there is little doubt that the disease is poverty-related (Alvar *et al.* 2006). In Bihar state, one of the economically most deprived states in India, 80% of the families in VL-affected villages were found to belong to the poorest two quintiles in terms of wealth distribution

[1] www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/index.html

(Boelaert *et al.* 2009). The characterisation of a typical VL case as the 'poorest of the poor' should therefore be taken fairly literally.

VL is a deadly disease if left untreated and one that can have a disastrous impact when it strikes a non-immune population. In Sudan, a VL epidemic caused major disruption to a famine-stricken society when, between 1984 and 1994, an estimated 100,000 cases died in the Western Upper Nile province (Griekspoor *et al.* 1999). VL often has profound effects even when endemic. The reported incidences of VL in endemic communities vary between two cases/1000 person-years in Kenya (Schaefer *et al.* 1995) to 14 cases/1000 person-years in Ethiopia (Ali & Ashford 1994) and 40 cases/1000 person years in an endemic community in eastern Sudan (Zijlstra *et al.*, 1994). Similar incidences have been observed in endemic areas of Asia (Rijal *et al.* 2010; Singh *et al.* 2010a). VL can suddenly 'unfold' without being noticed for years, as was recently documented in the Bakool region of Somalia, where VL had never previously been reported (Marlet *et al.* 2003).

Despite the considerable health burden posed by VL, there have been few attempts to quantify the economic impacts of the disease in affected communities. Every member of a household where a VL case occurs may lose many days of productive life. This loss, when added to the costs of treatment, may push an already poor household further into poverty (Adhikari *et al.* 2009), reduce food security and keep children from school. As with HAT, the high expected costs associated with a case of VL may deter the search for treatment. In 1997, the socio–economic characteristics of a cohort of 938 parasitologically-confirmed cases of VL from Bihar were investigated (Thakur 2000). Most (75%) of these cases were classified as poor (with daily incomes below U.S.$1.00), most (82%) were engaged in agriculture and/or animal husbandry, and most (77%) lived in mud or grass-covered houses. Delays in the seeking of medical care were considerable, with only 33% of the cases attending a healthcare facility within a month of the onset of their symptoms.

Over the last decade there have been at least seven attempts to estimate the financial and economic costs incurred by VL cases in India (Meheus *et al.* 2006; Sarnoff *et al.* 2010; Sundar *et al.* 2010a), Nepal (Sharma *et al.* 2004; Rijal *et al.* 2006; Adhikari *et al.* 2009) or Bangladesh (Sharma *et al.* 2006). The results of these studies unequivocally show that VL puts a considerable economic burden on the household of a case, with the cost of just one episode of VL exceeding the annual per-capita income. The estimates of the total cost of care incurred by the household of a case, including the direct and indirect costs, varied from U.S.$113.60 (Rijal *et al.* 2006) to U.S.$232.10 (Adhikari *et al.* 2009). The largest cost driver was found to be the income lost because of illness (i.e. an indirect cost), which may represent up to 60% of the total household cost (Meheus *et al.* 2006). The relative importance of income loss is explained by several factors. The mean time period between the onset of symptoms and the first presentation by the case at a formal health facility is often very long — Hasker *et al.* (2010) found it to be about 40 days — and the case is usually unable to maintain their normal productive activities until treatment is completed. In addition, the household members who care for the case are also diverted away from their usual means of income generation. The direct costs of drugs or medical supplies are often another important contributor to total costs. Although treatment is generally provided free of charge at public health facilities, such facilities (particularly those in India and Bangladesh) may not have the necessary drugs in stock, forcing households to buy drugs from private pharmacies, where the drugs may cost more than three times their official price (Sharma *et al.* 2006). Sometimes households may also need to purchase the medical supplies needed for the administration of the drugs, such as intravenous sets. As described by Adhikari *et al.* (2009), household expenditure on VL may be catastrophic. Coping strategies including the use of savings and the sale of assets and livestock, although the latter tends to reduce further the livelihood of the VL-affected households. More than 80% of such households investigated by Sarnoff *et al.* (2010) took a loan to pay for the costs of care, even though the interest payable on such a loan may exceed the amount loaned (Sharma *et al.* 2006; Adhikari *et al.* 2009).

There appears to be no published information on the economic impact of VL in East Africa or Latin America, although one relevant study is currently in progress in Sudan (A.A. Abuzaid, unpubl. obs.).

A few studies have addressed the choice of the most cost-effective strategy for VL control. In the first published cost-effectiveness analysis for VL, Griekspoor *et al.* (1999) tried to answer the question whether VL control was cost-effective in an emergency setting, in comparison to other relief measures (such as diarrhoea control). They estimated that, in a relief programme in Sudan, VL treatment cost U.S.$18.40 for each disability-adjusted life-year (DALY) averted (with an uncertainty range of U.S.$13.53–U.S.$27.63) and U.S.$595 for each life saved. The mean cost of the intervention was U.S.$394/treated VL case. As any health intervention costing less than U.S.$25/DALY averted is considered 'very good value for money' by the World Bank, Griekspoor *et al.* (1999) concluded that, at least in the local conditions, their treatment programme was cost-effective. Even more encouragingly, these estimates of cost-effectiveness were based on the use of branded sodium stibogluconate (i.e. Pentostam™; GlaxoSmithKline, Brentford, U.K.), at a mean cost of U.S.$100 per patient. The control programme has since switched to the use of generic antimonial drugs, which reduce drug costs by a factor of 5. Although generic antimonials have been shown to be effective in East Africa (Veeken *et al.* 2000) and to be cost-effective in

areas where the frequency of cure following antimonial treatment exceeds 94% (Vanlerberghe *et al.* 2007), they are, however, no longer recommended in India and Nepal because of high frequencies of failure (Sundar *et al.* 2000; Rijal *et al.* 2003).

Recently a number of therapeutic breakthroughs have occurred, including the clinical development of miltefosine as the first oral drug for VL (Sundar *et al.* 2002), the evaluation of paromomycin in combination therapy (Thakur *et al.* 2000; Melaku *et al.* 2007) and the development of a single-dose regimen of liposomal amphotericin B (Sundar *et al.* 2010b). Although a single dose of liposomal amphotericin B has been shown to be very effective, the cost of the drug still poses a barrier to its routine use as a first-line treatment (unless the international community is willing to finance the drug). While the VL-elimination initiative has adopted miltefosine as a first-line treatment, parasite resistance to both this drug and paromomycin may develop, as shown experimentally (Seifert *et al.* 2003). To safeguard the few effective drugs that currently exist from the emergence of resistance, combination therapies are increasingly being advocated, with the results from phase-III trials of combinations eagerly awaited. The additional advantages of combination therapies include shorter treatment durations and lower costs to both the public-health system and affected households. Olliaro *et al.* (2009) compared the cost-effectiveness of a combination of liposomal amphotericin B and miltefosine with those of various monotherapies and found that, at a cost of U.S.$124–U.S.$160/death averted, the combination therapy was a 'competitive' alternative. Another cost-effectiveness study for the Indian subcontinent, conducted from a societal perspective (including both health system and patient costs), was recently completed by Meheus *et al.* (2010). This study compared three plausible combination therapies with all possible monotherapies and showed that 10 days of treatment with a miltefosine–paromomycin combination was the most cost-effective treatment strategy (costing U.S.$92/death averted), followed by a combination of liposomal amphotericin B with either paromomycin or miltefosine.

CONCLUSIONS

The fact that sleeping sickness and human visceral leishmaniasis have such low profiles, at both the national and international level, has prevented health systems in affected countries from allocating the appropriate resources for the control of these diseases. The Millennium Development Goals, with their emphasis on poverty reduction, provide a unique 'window of opportunity' to raise awareness about these diseases, and other NTD, at international level. A supranational approach to surveillance and control — as in the VL-elimination initiative in South Asia — might well be justified, as foci are often spread across borders. The results of

studies on health economics can support disease-control initiatives and help strengthen the case for greater investment in research on, and control of, VL, HAT and other poverty-related diseases.

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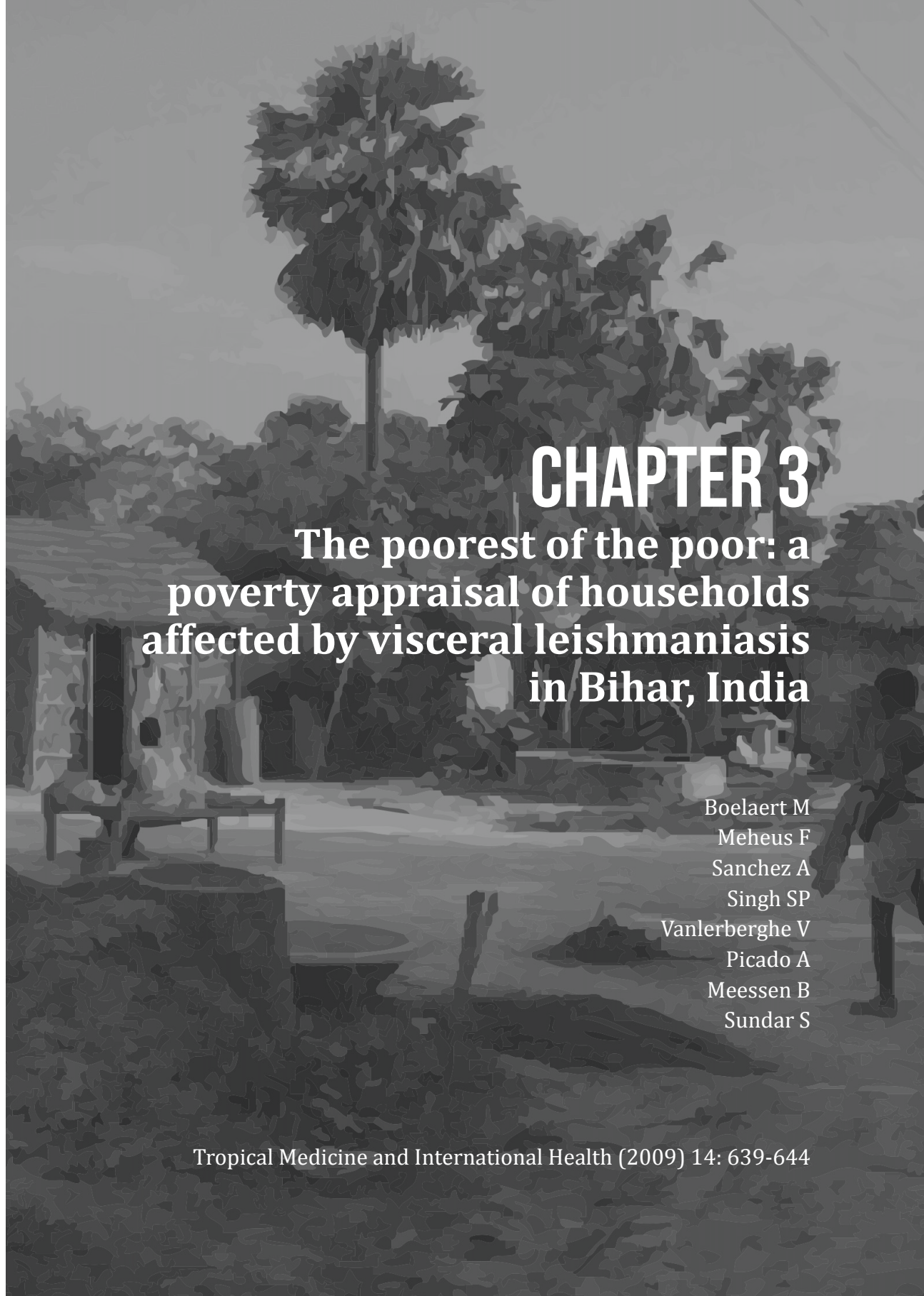

CHAPTER 3

The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India

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ABSTRACT

Objective

To provide data about wealth distribution in visceral leishmaniasis (VL)-affected communities compared to that of the general population of Bihar State, India.

Methods

After extensive disease risk mapping, 16 clusters with high VL transmission were selected in Bihar. An exhaustive census of all households in the clusters was conducted and socio-economic household characteristics were documented by questionnaire. Data on the general Bihar population taken from the National Family Health Survey of India were used for comparison. An asset index was developed based on Principal Components Analysis and the distribution of this asset index for the VL communities was compared with that of the general population of Bihar.

Results

83% of households in communities with high VL attack rates belonged to the two lowest quintiles of the Bihar wealth distribution. All socio-economic indicators showed significantly lower wealth for those households.

Conclusion

Visceral leishmaniasis clearly affects the poorest of the poor in India. They are most vulnerable, as this vector-born disease is linked to poor housing and unhealthy habitats. The disease leads the affected households to more destitution because of its impact on household income and wealth. Support for the present VL elimination initiative is important in the fight against poverty.

INTRODUCTION

Visceral leishmaniasis (VL) or kala-azar is a parasitic disease affecting an estimated 500,000 new cases per year, mostly in the Indian subcontinent and East Africa, though this figure is subject to substantial uncertainty. VL usually occurs in small clusters in remote areas with poor access to health services and exact case numbers are poorly documented. In prospective studies of such clusters in East-Africa, incidence rates of VL varied between 2 / 1000–40 / 1000 person-years (Ali & Ashford 1994; Zijlstra *et al.* 1994; Schaefer *et al.* 1995). Incidence rates reported from the Indian subcontinent in 2001–2003 were in similar ranges (Singh *et al.* 2006). These rates are comparable to or higher than the incidence rates of tuberculosis at community level, but cannot be extrapolated to the population at large beyond the boundaries of the clusters where active VL transmission occurs, whereas tuberculosis is more homogeneously distributed. Nonetheless, VL can have a disastrous impact when an epidemic strikes a non-immune population. In famine-affected Southern Sudan, a VL epidemic caused the death of an estimated 100 000 people between 1984 and 1994 in Western Upper Nile Province (Seaman *et al.* 1996). Visceral leishmaniasis is nowadays considered as one of the 'most neglected diseases', a term coined to highlight the lack of innovation in both its clinical management and control (Trouiller *et al.* 2001). Several authors also concur that VL is a poverty-related disease, though the importance of VL as a hindrance for economic development is still not fully recognized (Wijeyaratne *et al.* 1994).

Advocates for the control of the disease will often claim that VL disproportionally affects 'the poorest of the poor' (Alvar *et al.* 2006), but this statement was not substantiated so far, apart from showing that VL patients live below the poverty line (Desjeux 1996), but so do many of their non-affected fellow citizens. In the context of a community intervention trial on the effect of long-lasting impregnated bed nets in the prevention of VL conducted in Bihar, India (the KALANET trial, see http://www.kalanetproject.org), we studied the socio-economic profile of the households living in areas with high VL endemicity and compared it to that of the general population of Bihar.

METHODS

Study area

Within the framework of the KALANET community intervention trial (Clinicaltrials.gov CT-2005-015374), we started in February 2006 to identify eligible VL clusters (i.e. well-defined communities with 350–1500 inhabitants) with a high incidence of VL in Muzaffarpur district (3.7 million inhabitants) in the northern part of Bihar State, India. Preliminary information

about villages with large numbers of VL cases was obtained from the public health system (Primary Health Centres, District Hospital and Medical College) and private and charitable hospitals. By the end of March 2006, we had identified 35 clusters with the highest reported number of VL cases in Muzaffarpur district. This was followed by a house to house survey of these clusters in May 2006 to evaluate the incidence rate of VL during the preceding three years (3.5 years in some clusters; 2003–2005 / 06). From these, 16 study clusters were selected (Table 1), based on five characteristics: (i) Reporting VL cases in each year of the 3-year-period, thus showing continuous transmission of the disease; (ii) an average of at least 0.8% VL incidence rate over the past 3 or 3.5 years; (iii) highest incidence rates; (iv) population between 350 and 1500; (v) minimum distance between any two clusters of 1 km.

Table 1: Selected clusters with high visceral leishmaniasis (VL) incidence in Muzaffarpur district, Bihar

Cluster	Population	VL incidence			Annual incidence rate
		2003	2004	2005/2006*	per 100 person/years
1*	779	20	1	6	0.99
2	1210	7	12	27	1.27
3	716	6	9	5	0.93
4	601	6	6	9	1.16
5*	605	6	7	11	1.13
6	517	2	8	11	1.35
7*	648	6	3	37	2.02
8	630	7	8	12	1.43
9*	850	1	4	31	1.21
10*	559	6	10	24	2.04
11	464	11	2	4	.122
12*	728	5	10	21	1.41
13*	459	5	6	11	1.37
14*	1150	11	13	32	1.39
15	350	8	5	4	1.62
16*	1051	4	15	65	2.28

* Figure represents incidence calculated over 3.5 years; these are clusters where the number of VL cases during the first 6 months in 2006 was also collected

Socio-economic data

In the 16 study clusters, extensive household (HH) and individual data were collected in August–September 2006 on pre-designed questionnaires that included standardized questions on socio-economic items in an exhaustive census of the households. Information was collected from 2013 households and double-entered into an Access database.

As comparison data, we used data from the third National Family Health Survey (NFHS-3) of India (authorized on 26/11/2007) to document the socioeconomic status of the households in the state of Bihar, to which the above clusters belonged. The Indian NFHS are nationwide surveys conducted with a representative sample of households throughout the country, which provide data on population and health indicators such as fertility, family planning, infant and child mortality, maternal and child health, nutrition or morbidity and health care. These surveys are implemented by the International Institute for Population Sciences of Mumbai, and belong to the Monitoring and Evaluation to Assess and Use Results (MEASURE), Demographic and Health Surveys (DHS) project, composed of several partners who provide technical assistance and funding to more than 200 surveys in 75 countries since 1984. The Indian NFHS-3 was conducted between November 2005 and August 2006, with an overall sample size of 109 041 households (International Institute for Population Sciences & Macro International 2007) and 2997 households from the state of Bihar. We used the latter data.

Asset index

To allow poverty ranking of the Bihar as well as the households living in areas with a high VL endemicity, we chose an approach based on an asset index, which has been widely used as a proxy to measure poverty when income and expenditure data are of poor quality or not available. Data on ownership of durable assets in the households, characteristics of the habitat and access to basic services are the indicators most commonly collected and used to construct a single 'asset index'. This measure reflects the long-run household wealth or living standard, so unequal measures of the asset index can be considered as proxies for inequalities in long-run wealth (Filmer & Pritchett 2001; Falkingham & Namazie 2002; McKenzie 2005). We selected nine indicators, reflecting four dimensions of longrun wealth, to be included in the asset index (Table 2).

Table 2: Indicators included in the asset index

Category	Asset indicator
Housing structure	Type of house: Kachha; Semi-pucca; Pucca
Household access to utilities and infrastructure	Main type of fuel used for cooking : traditional (animal dung / agricultural crop waste / straw, shrubs, grass) or modern (gas, electricity or petrol)
	Whether the household has electricity or not
Productive assets	Whether the household has a bicycle or not
	Whether the household has a motorcycle / scooter or not
	Whether the household has a car / tractor or not
Non-productive assets	Whether the household has a radio or not
	Whether the household has a television or not
	Whether the household has a cot / bed or not

We used Principal Components Analysis (PCA) to aggregate the information from the different indicators in order to create an asset index that explained 35.4% of variance. The analysis was performed with spss v.15.0 software. PCA is a multivariate statistical technique that assigns weights to the indicators so to create the weighted linear combination of the variables that accounts for the largest amount of the total variation in the data (Kleinbaum *et al.* 1988; Vyas & Kumaranayake 2006). PCA has been applied by several authors to create indices of relative poverty (Filmer & Pritchett 2001; McKenzie 2005; Vyas & Kumaranayake 2006; Zeller *et al.* 2006; Morris *et al.* 2007) with the underlying assumption that relative poverty explains the maximum variance in the variables.

When the indicators included in the PCA differ in their measurement scale, they should be converted into standardized variables, so that the resulting index can be represented by the formula:

$$A_i = f_1 \frac{(a_{i1} - \bar{a})}{s_1} + \cdots + f_n \frac{(a_{in} - \bar{a}_n)}{s_n}$$

where Ai is the asset index of the i th household, f1 is the weight for the first indicator, ai1 is the i th household's value for the first indicator and _a1and s1 are the mean and standard deviation of the first indicator over all households (Filmer & Pritchett 2001).

We used the asset index score to classify the households from Bihar state in wealth quintiles. Using the formula mentioned above, we applied the weights obtained with PCA to the indicator values of the households living in areas with a high VL endemicity (KALANET project clusters),

in order to place them within the wealth quintiles of the state of Bihar. Student's t-test was used to compare asset ownership between Bihar and highly endemic VL clusters.

Ethical approval

The study was conducted as part of the KALANET community intervention trial (Clinicaltrials.gov CT-2005-015374), for which ethical clearance was obtained from the Institutional Review Boards at Banaras Hindu University and the Institute of Tropical Medicine.

RESULTS

The distribution of the asset index score for the general population of the State of Bihar is shown in Figure 1. The asset index is a measure of relative poverty, so the lower the score, the poorer the household relative to all others with higher scores.

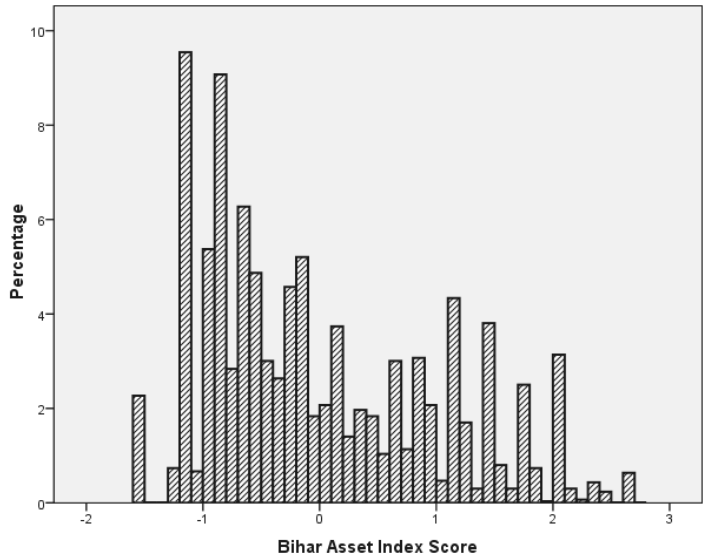

Figure 1: Histogram of the Bihar Asset Index

Figure 2 shows how households from highly endemic VL areas fit within the wealth distribution of the households in Bihar based on NFHS-3 data. The number of households in the top two quintiles (8.3%) is very low, and the vast majority of households in VL endemic areas are situated in the two poorest quintiles of the wealth distribution of Bihar (83.3%).

Figure 2: Distribution of wealth of households living in highly endemic VL clusters within the socioeconomic quintiles of all Bihar households

Table 3 shows the distribution of the socio-economic indicators included in the asset index for the Bihar and the populations living in areas with a high VL endemicity. There are significant differences between both populations in all the indicators, pointing out the extremely low numbers of households with appropriate housing and access to basic services and assets in the communities affected by kala-azar.

Table 3: Socio-economic indicators for Bihar and highly endemic visceral leishmaniasis (VL) cluster populations

Asset indicator	Bihar		Highly endemic VL cluster		
	n	(%)	*n*	(%)	*P*-value
Type of house					
Kachha	794	(26.5)	1418	(70.4)	< 0.0001
Semi-Pucca	1248	(41.6)	477	(23.7)	< 0.0001
Pucca	955	(31.9)	118	(5.9)	< 0.0001
Traditional* cooking fuel	1639	(54.7)	1845	(91.7)	< 0.0001
Electricity	1212	(40.4)	193	(9.6)	< 0.0001
Bicycle	1646	(54.9)	839	(41.7)	< 0.0001
Motorcycle/scooter	338	(11.3)	46	(2.3)	< 0.0001
Car/tractor	96	(3.2)	10	(0.5)	< 0.0001
Radio	983	(32.8)	197	(9.8)	< 0.0001
Television	864	(28.8)	136	(6.8)	< 0.0001
Cot/bed	2722	(90.8)	1556	(77.3)	< 0.0001
Total	2997	(100.0)	2013	100.0)	

* Traditional = Animal dung, agricultural crop waste, straw, shrubs or grass

Other socio-economic indicators (not included in the asset index) such as education, caste or religion of the head of the household also show significant differences (Table 4). Higher percentages of illiteracy are found amongst the heads of the households living in areas with a high VL endemicity. There was a stronger presence of Scheduled Castes (SC), Scheduled Tribes (ST) and Other Backward Castes (OBC), the lower castes in India, in the clusters affected by high VL transmission.

Table 4: Socio-economic characteristics of heads of households

Variable	Bihar		Highly endemic VL cluster		
	n	(%)	*n*	(%)	*P*-value
Caste*					
SC/ST	503	(16.8)	440	(21.9)	< 0.0001
OBC	1792	(59.8)	1381	(68.6)	< 0.0001
Other	697	(23.3)	175	(8.7)	< 0.0001
Illiterate	1588	(53.0)	1354	(67.3)	< 0.0001
Religion					
Hindu	2477	(82.6)	1801	(89.5)	< 0.0001
Muslim	513	(17.1)	212	(10.5)	< 0.0001
Total	2997	(100.0)	2013	(100.0)	

* SC/ST: scheduled caste/scheduled tribe; OBC: other backward caste

DISCUSSION

This study is the first to show clearly that VL affects the poorest of the poor. Bihar state is known to be one of the poorer states of India, with 40% of its population living below the poverty line, while the national average is 29% (World Bank 2008). Our data indicate that the communities with high and active VL transmission over the past three years are situated at the lower end of the wealth distribution of Bihar state.

The fact that data from two different surveys were used to construct the asset index can be considered a limitation, though both were carried out contemporaneously and worked with an almost similar set of standard questions. PCA was used to derive the weights assigned to the assets included in the index. Filmer and Pritchett (2001) showed that a PCA-based index performed as well as consumption expenditure, and more recently a study comparing different methods to assign weights to the indicators concluded that PCA was a suitable method (Howe *et al.* 2008) although the weighing method might be of less importance than the data used.

There exists ample evidence that poverty and ill-health are intertwined, with poor people suffering worse health and having more limited access to health care. Likewise, ill-health may lead to a loss of income through absence from work and high health care costs (Wagstaff 2002), driving poor households even further into poverty (Bloom & Canning 2003). As described by Alvar *et al.* (2006), the relationship of VL to poverty is complex and additional research that leads to a better understanding on the interaction between VL and poverty is needed. In the Indian subcontinent, infection risk is clearly related to poor housing conditions and sanitation, as the sand fly vector Phlebotomus argentipes breeds in cracks of mud-plastered houses and moist soils. The disease has a chronic course and is fatal if left untreated; therefore households often sell their assets and take loans to pay for health care and expensive drugs which may result in significant impoverishment (Desjeux 1996). Moreover in every family with a VL case, the severely debilitating disease has a significant impact on earnings and consumption with many days of productive life lost due to illness. Two studies from Nepal and a study from India showed how the total cost of a VL episode to affected families exceeded their average annual per capita income and how households either sold part of their livestock or took loans to cover the costs (Adhikari & Maskay 2003; Rijal *et al.* 2006; Meheus *et al.* 2006).

Although our results have shown that in Bihar communities with high VL incidence are considerably poorer than the rest of the state, this does not necessarily imply a causal relationship between VL and poverty. Wealth differences between VL affected clusters and the rest of Bihar could also be explained by other factors such as differences in ecological conditions and economic growth within Bihar or individual differences such as caste, literacy rates and land ownership. Comparing VL endemic clusters with for example North Bihar only, which would have taken into account regional wealth differences to a certain extent, was not possible since the NFHS-3 does not include district level identifiers for reasons of confidentiality (the survey also measures HIV-status). Even so, this does not alter the findings presented in this paper.

Though global case numbers of VL might rank lower than those of HIV/AIDS, malaria and tuberculosis, the social and economic implications of VL in affected communities are profound. VL clearly affects the poorest of the poor in India and adds to their destitution. This study suggests that current and future preventive measures for such a deadly disease need to be subsidized or provided free to the majority of households living in VL affected areas of India, or else they might prove futile. Support for the present VL elimination initiative is important in the fight against poverty.

ACKNOWLEDGEMENTS

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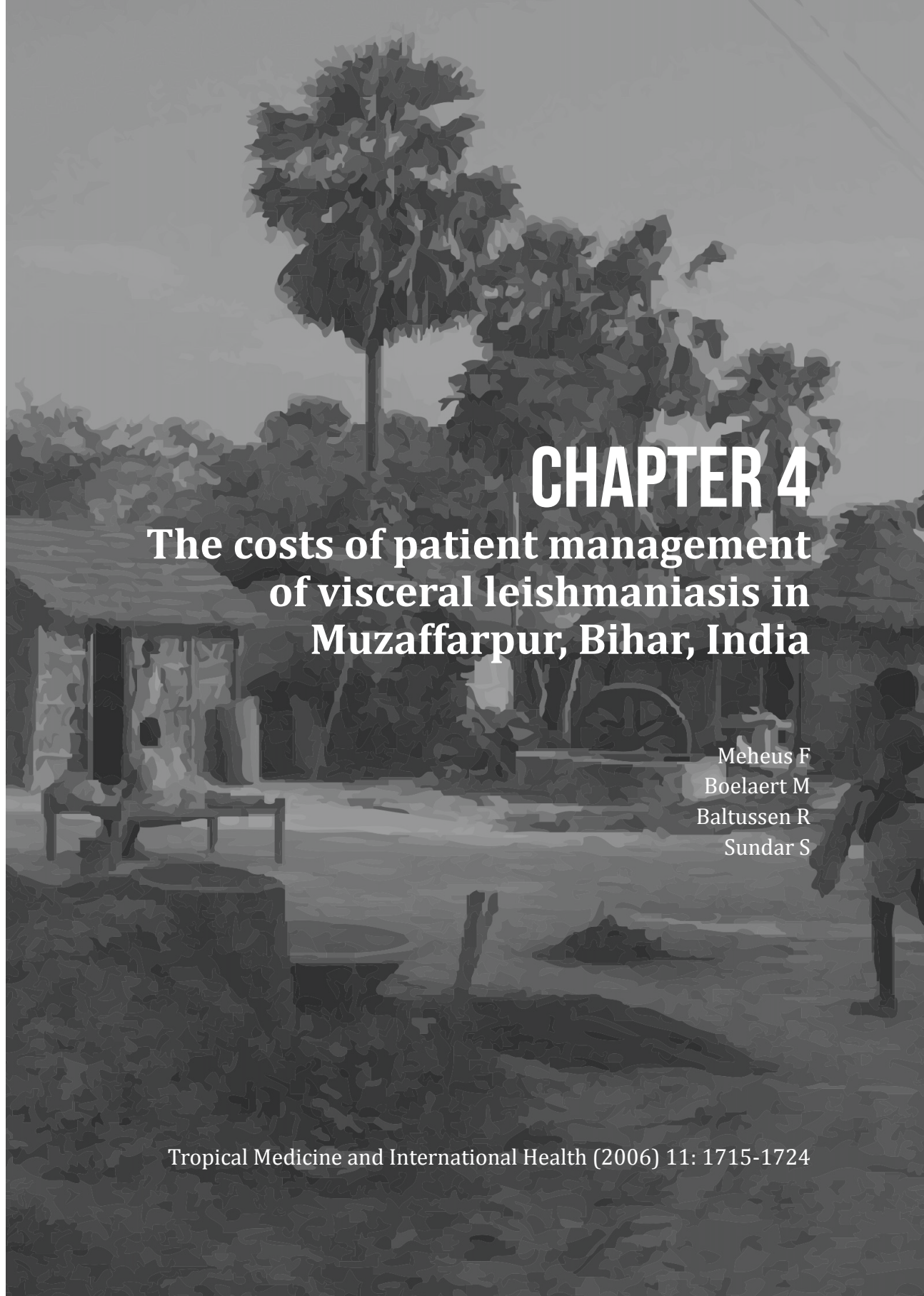
PART II

The economic impact and costs of patient management of visceral leishmaniasis



CHAPTER 4

The costs of patient management of visceral leishmaniasis in Muzaffarpur, Bihar, India

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Baltussen R
Sundar S

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ABSTRACT

Objective

To identify and quantify the direct and indirect economic cost of treatment for visceral leishmaniasis (VL) with conventional Amphotericin B deoxycholate, currently the first-line treatment in Muzaffarpur.

Methods

Costs of patient management for VL were estimated from a societal and household perspective by means of a questionnaire designed for this study, interviews and financial reports.

Results

The total cost of care per episode of VL from the societal perspective was estimated at US$355, equivalent to 58% of annual household income. The largest cost category was medical costs (55%), followed by indirect costs (36%) and non-medical costs (9%). The cost from the household perspective was equivalent to US$217. The largest cost category was indirect costs (59%), followed by medical costs (27%) and non-medical costs (15%). Loss of income because of illness and hospitalization and expenses for drugs were the largest cost components.

Conclusions

The economic costs related to VL are substantial, both to society and the patient. Public health authorities in Bihar should focus on policies that detect VL in the early stage and implement interventions that minimize the burden to households affected by VL.

INTRODUCTION

Visceral leishmaniasis (VL) or Kala-azar is a life-threatening disease if left untreated. Ninety per cent of all cases occur in only five countries: Bangladesh, Brazil, Nepal, Sudan and India (WHO 2000); with India accounting for half of the cases and about 90% of Indian patients living in the state of Bihar (Sundar *et al.* 2001).

Visceral leishmaniasis in India is caused by Leishmania donovani and is transmitted by the bite of an infected phlebotomus female sandfly. Patients infected with VL usually present prolonged fever, diarrhoea, cough, abdominal pain, enlarged liver and/or spleen, nose bleeds and severe loss of weight. Complications of VL include post-kala-azar dermal leishmaniasis (Guerin *et al.* 2002).

Pentavalent antimonial compounds (Sbv) is the recommended treatment in all parts of the world except for Bihar where 64% of previously untreated patients showed unresponsiveness to Sbv, even with the WHO recommended treatment of 20 mg/kg/day for 30 days (Murray 2000; Sundar 2001). Conventional Amphotericin B deoxycholate is now the drug of choice in Bihar, with 15–20 infusions of 1 mg/kg given either on a daily or alternate basis enforcing prolonged hospitalization (Sundar *et al.* 2004). Amphotericin B shares drawbacks with Sbv such as length of therapy and parental administration; it is more expensive and requirements of infusions and close monitoring because of its potential toxicity necessitate hospitalization for the duration of treatment (Murray 2000). Over the past years, tangible progress has been made and has offered some promising alternatives to current treatments: Miltefosine has recently been registered in India and is the first oral drug for VL and Paromomycin, which is currently being tested in India, seems a promising low-cost alternative to current treatment with Amphotericin B in Bihar (Murray 2004).

Whilst the literature on clinical studies of treatment options for VL steadily increased in the 1990s (Olliaro *et al.* 2005), there has been little effort to quantify the economic consequences of the disease on the affected population. This paper presents the results from a costing analysis in Muzaffarpur, Bihar (India). The objectives of the study were to identify/quantify the economic cost of treatment for VL with conventional Amphotericin B deoxycholate, currently the first-line treatment in Muzaffarpur. Costs in this study are defined in terms of opportunity cost (or economic cost), which is the value of resources foregone that could have been used elsewhere. When opportunity costs are estimated, all inputs are valued, even those for which there was no monetary cost, such as donations or inputs that have been paid for below market price. Costs associated with patient management of VL include direct medical costs borne by the provider, the patient and its family, direct non-medical costs borne by patients and family and

indirect costs related to time lost from productive work borne by patient and family and were estimated from the perspective of society as a whole and that of the household. The analysis of household costs is important because we believe that as VL mainly affects individuals from the lowest socioeconomic class, treatment of the disease can play an important role in poverty reduction and should therefore try to minimize the cost to patients. Furthermore, over the past years there have been major advances in the development of anti-leishmanial drugs that have a different impact on costs (including costs to the patient). It is therefore important to analyse all costs associated with VL patient management from different perspectives. The findings from this study can be useful for further costing studies and for evaluating the recently developed alternatives with the current treatment for VL in Bihar. The paper is organized as follows: first we present the conceptual framework used for the analysis and the process of patient management, data collection and cost estimation. The conceptual framework draws on guidelines for cost and cost-effectiveness analysis in general (Creese & Parker 1994; Tan-Torres Edejer *et al.* 2003) and for particular diseases (Asenso-Okyere & Dzator 1997; WHO 2005). The subsequent section presents the results of our cost analysis from the societal as well as from the patient perspective, and discusses the implications of our findings for VL control.

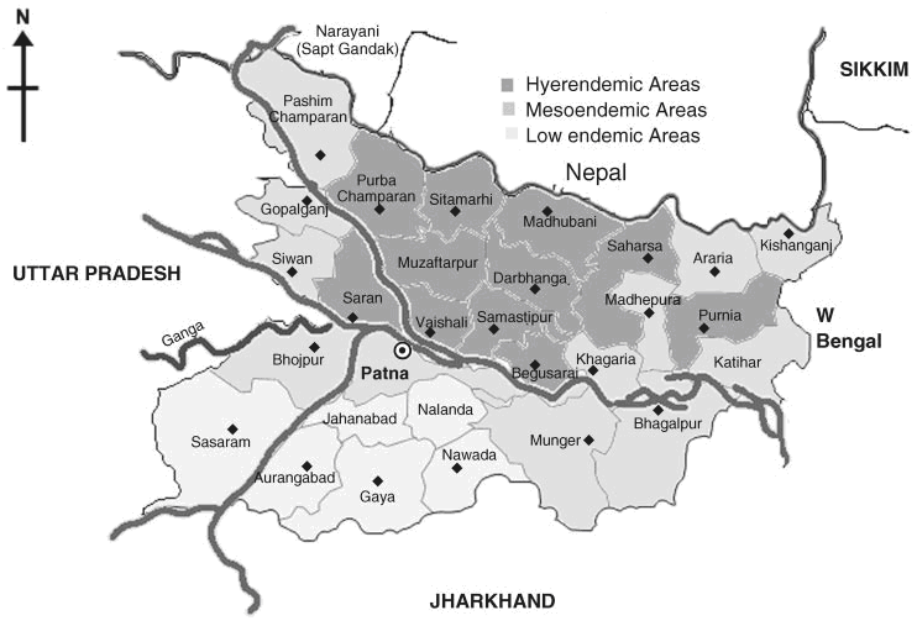

Figure 1. Map showing endemicity of visceral leishmaniasis in Bihar.
Source: Sundar (2001)

METHODS

Study site

Data were collected in July and August 2005 at the Kala-azar Medical Research Centre (KAMRC). The KAMRC is a hospital that only provides care for VL and is run by a non-governmental charitable Sitaram Memorial Trust supported by grants and private donations. The hospital is located in Muzaffarpur 75 km away from the state capital of Patna. Muzaffarpur is the second largest city in Bihar (India) and is considered a highly endemic area of VL with a high degree of antimony resistance (Sundar 2001).

The region is the third most densely populated area of India and performs considerably worse with regard to poverty indicators compared to the rest of India. An estimated 40% of the population lives below the poverty line of 1 US$ per day. The vast majority of the workforce (80%) is employed in agriculture with a predominance of subsistence agriculture (World Bank 2005). The total population in the district of Muzaffarpur is around 3.75 million inhabitants of whom the vast majority (90%) lives in a rural setting (Figure 1).

Process of patient management

In order to understand the process of data collection and correctly interpret the estimated costs a description of a standard patient management follows. First a patient suspected of having VL presents spontaneously or is being referred to the outpatient section of the KAMRC. Confirmation of Kala-azar is based on typical clinical and laboratory features like fever, splenomegaly, pancytopenia and diagnostic tests such as presence of parasites (asmastigotes) in spleen aspirate smears and/or positive rK39 rapid strip test. If the patient has Kala-azar, he/she is admitted to the hospital for the full duration of treatment. Up to this point, all costs (travel, food, diagnostic tests) are paid out-of-pocket by the patient. Once admitted, the patient receives conventional Amphotericin B deoxycholate on a daily or alternate (every 2 days) basis depending on the physiological characteristics of the patient. The patient is also regularly submitted to laboratory investigations to test for toxicity and side-effects related to the drug. On admission the patient only pays a nominal admission fee to the hospital and other services (e.g. tests) are provided free of charge. The drugs for VL (Amphotericin B) have to be retrieved by the patient or a family member outside the hospital at a local private pharmacy at a pre-negotiated subsidized cost and brought back to the hospital where it is administered intravenously by medical personnel. The i.v. sets and related equipment for the i.v. injections as well as the laboratory tests and the daily bed fee are provided free of charge by the hospital to the patient. Similarly medical supervision, nursing are also provided free of charge. During hospitalization, in most cases one or more family members stay with the patient on a permanent

basis. Once discharged, the patients comes back to the hospital after the 1st, 3rd, 6th and 12th month to check for side-effects and relapse. In this study, we only analysed the costs related to diagnosis and treatment of VL, and not the costs incurred by the patient after discharge.

Cost categories

The costs associated with patient management of VL can be direct (medical and non-medical) and indirect (time losses).[1]

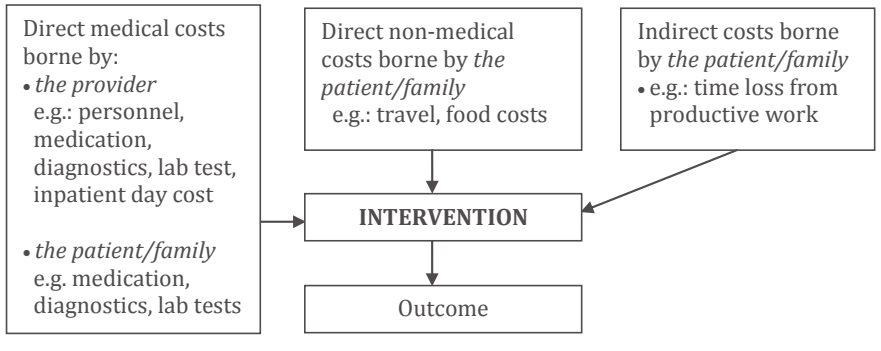

Figure 2. Costs of patient management of Visceral Leishmaniasis
Source: Adapted from Brouwer et al (2001)

Direct costs

Direct medical costs associated with VL include costs borne by the provider to deliver the intervention (i.e. provider costs) and costs borne by the patient and family to receive treatment (i.e. household costs). The provider costs are the resources used to implement and make the treatment for VL available. These include personnel costs (doctors, nurses), overhead costs (administration, maintenance and electricity), infrastructure (buildings), medical equipment (i.v. sets, syringes and needles), medication, laboratory tests and hotel costs (e.g. bed linen).

Costs borne by the household are the resources used to access the treatment for VL and can be medical or nonmedical. Direct medical costs include out-of-pocket expenditures on consultation fees, diagnostic tests and payment for VL drugs. The direct non-medical costs borne by the patient/family are travel costs to and from the health facility and drug stores and food expenses (Sauerborn *et al.* 1991; Barnum & Kutzin 1993; Asenso-Okyere & Dzator 1997; Duraisamy *et al.* 2006).

[1] A third category that is sometimes mentioned in the literature are the intangible costs. These are costs related to anxiety and pain to the patient and relatives and can be captured with non-monetary measures such as QALYs. These were not included in this study because of the difficulty to estimate these.

Indirect costs

Indirect costs refer to the value of time losses because the patient is unable to carry out his/her normal productive activities because of ill-health associated with VL. Time losses include travel time to and from the hospital and drugs stores, time lost at the hospital (e.g. consultation) and the time of hospitalization. The valuation of these time losses is a controversial issue. It is generally recommended not to include them in the analysis unless their exclusion may introduce bias into the estimates (Hutton & Baltussen 2005). As patients and their relatives require prolonged and repeated contact with the system, we valued the time of lost work with the human capital method where earnings (i.e. income) are used as a proxy of the opportunity cost of lost time[2]. These time losses can be incurred by the patient and by the family members caring for the patient at the hospital (Figure 2).

Data collection and cost estimation

Information on provider's cost was derived from annual financial reports for the year 2003–2004 of the medical centre and from the hospital administrator. These financial reports only present aggregated financial expenditure lines. This was not considered a problem as the KAMRC is fully dedicated to VL care, and all expenditures by the hospital can be attributed to the VL programme. Methods to allocate the overhead costs to different department or programmes were therefore not necessary. Items purchased by the hospital below market rates were corrected using market prices to reflect economic costs. For example the cost of the hospital building was valued with the rental value of a similar space in the same location (Hutton & Baltussen 2005).

Data on the patient's direct and indirect costs were obtained from medical records (e.g. to retrieve the number of lab tests undergone), medical personnel and from patients and their relatives with a structured questionnaire designed for this study. The patient, the head of the household or a principal respondent was interviewed. The questionnaire collected data on demographic characteristics (age, relation to head of household, household size, education and literacy) and socioeconomic characteristics (occupation, monthly income of patient and of family members staying with the patient at the hospital as well as household income), on direct medical costs (consultation fees, laboratory tests and drugs) and direct non-medical costs (travel expenses, food costs) incurred by the patient and accompanying relatives. The questionnaire also included questions on health-seeking behaviour and costs prior to admission at the KAMRC and on additional expenditures to meet the costs of treatment: loans taken and

[2] The main approaches to value the time of lost work are the human capital method, the friction cost method and willingness to pay methods such as revealed preference studies and stated preference studies. For a discussion of these and other methods see Koopmanschap *et al.* (1995), Drummond *et al.* (1997) and Sculpher (2001).

interest charged, origin of the loan (moneylender, relative, village person, etc.) and assets sold (livestock, land, durables).

Direct medical costs to the patient were calculated by taking an ingredient approach (Creese & Parker 1994). This involves asking the patient or the principal respondent the quantities consumed and price paid for each cost item (mainly drugs and laboratory tests). Patients or relatives purchase Amphotericin B at a subsidized price at the local private pharmacy. Because this situation is very specific to the KAMRC and evaluating costs from a societal perspective, this subsidized price was replaced by the market price (Hutton & Baltussen 2005). An ingredient approach was also taken when calculating travel costs. Travel costs consist of visits to and from the health facility and drug stores by the patient and/or relatives as well as visits received by the patient from family members during his/her hospitalization. The travel costs were assessed by asking the patient or principal respondent the cost for a one-way journey to the health centre. This amount was then doubled to obtain the total travel cost for one trip (Cho-Min-Naing & Gatton 2004). The travel costs are for the patient and accompanying relatives together as it was difficult for the respondent to separate them (e.g. rented car for unlimited number of passengers, young patients not paying for rickshaw). Food costs were assessed by asking the daily food cost for the patient and all family members staying permanently with the patient at the hospital and for family members from the same household visiting the patient. This amount does not include food brought from the household by visiting members as it was difficult to estimate this cost.

Indirect costs were calculated by asking for the monthly income of the patient, family members staying with the patient at the hospital and the rest of the household. In many cases, respondents could only give a daily income. This daily income was then multiplied by 30 (days) to calculate the monthly income. It was also assumed that this daily income was stable over the entire month. Because many households were employed in agriculture and thus earned a very small monetary income, the questionnaire included questions on the amount of agricultural produce and the market price of these crops to allow for estimation of a monthly income if these were to be sold. Same was carried out for output of livestock (e.g. milk from cattle). The sum of the patient's earnings and those of its family members constituted the average monthly household income. In the interpretation of costs, care was taken not to double count certain cost items such as hospital costs.

Study population and sample

Patients were selected from admission records. All patients admitted/or presenting for follow-up at the time of the study (between 23 July 2005 and 4 August 2005) were approached. Patients on follow-up visit were only included if they had been discharged no longer than 6 months to minimize recall bias. All patients received treatment with conventional Amphotericin B deoxycholate. Seventy-seven patients were approached. After explaining the objective of the study and the type of data required, all patients gave their consent to participate with the study. Of the seventy-seven patients, fifty patients belonged to the group of inpatients and 27 were follow-up patients. All costs were identified in terms of the local currency (1US$ is equivalent to INR 43.40 for the month July 2005 at the official exchange rate during the period of the study).

RESULTS

Demographic and socioeconomic profile of study participants

The surveyed patients were on average 16 years old (range 3–60 years). A majority of the patients were male (64%) and 18% of the patients were head of their household. The average size of the household was eight persons. Although, a majority of the patients (56%) reported having followed formal schooling with more educated men (33%) than women (23%), the average years of schooling was only 3 years. Twenty-six per cent of interviewed patients were engaged in agriculture and/or animal husbandry, 13% were working in salaried employment, 3%in business, 25%of the patients were students, 17% were engaged in domestic duties (cooking, cleaning, fetching water, wood, etc.). The remaining patients (16%) were not engaged in any productive activity because of their young age (median age 5 years.).

Of the patients earning a monetary income (n=30), 43% earned less than a dollar per day, 43% had an income between $1 and $2 and 14% earned more than $2 on a daily basis. The median household income on a monthly basis was 2200 rupees (range 500–9000).

Clinical and treatment characteristics of study participants

The median duration of hospitalization was 18 days which is lower than the standard length of hospitalization of 28 days reported in the literature because most patients (88%) in this study were treated with conventional Amphotericin B deoxycholate with infusions on a daily basis and were admitted to the hospital for the full duration of treatment. (Table 1).

Table 1: Clinical and treatment characteristics (*n*=77)

Variables	Median	(IQR[a])
Duration of hospitalization (# days)	18	(18-19)
Duration of illness (# days)	70	(24-90)
Number of vials per patient	8	(5-11)
Body weight (kg)	36	(20-45)

[a] Interquartile range

Costs from the societal perspective

Medical, non-medical and indirect costs associated with VL patient management are presented in Table 2. The total cost of care per episode of VL was estimated at 15 400 rupees and is equivalent to 58% of annual household income. The total *medical* cost over the period of hospitalization amounted to 8490 rupees. The 'accommodation' cost for hospitalization per patient was 2736 rupees and is an aggregate of personnel costs, overhead costs, infrastructure. The cost of investigations (diagnostic and laboratory tests) per patient was 2700 rupees. The median cost of drugs is 2334 rupees and consists of Amphotericin B (92%) and miscellaneous drugs (8%). The medical supplies amount to 720 rupees per patient and include i.v. sets and 5% dextrose water necessary for the intravenous injections of Amphotericin B. *Non-medical* costs amounted in total to 1410 rupees and consists of transportation costs (33%) and food cost (67%). The patient received on average four visits from members of the same household. In all cases a relative stayed permanently with the patient at the hospital: in 69% of the cases this was one relative, in 26% of the cases this were two relatives and in the remaining 5% three relatives stayed with the patient at the hospital.

The median loss of income to the patient and attendants was 5300 rupees. Other costs include the monthly interest payment on loans taken to meet the costs of VL treatment and amounted to 200 rupees.

Costs from the household perspective

Costs from the perspective of the household include out-of pocket expenditures and indirect costs incurred by the patient and their relatives (Table 2). All patients incurred substantial out-of-pocket expenditures to acquire treatment for VL. The main cost item for the patient is the drug cost which amounts to 2160 rupees. Consultation fees amounted to 170 rupees. The median cost of investigations purchased by the patients amounted to 180 rupees and consists of diagnostic tests only. The median transportation cost was 460 rupees. The median daily food cost for the patient and relative(s) staying permanently at the hospital was 50 rupees. The total amount of out-of-pocket payments by the patient (and relatives) over the entire length of hospitalization was 3920 rupees.

Table 2. Costs of patient management from societal and household perspective (rupees)

	Costs from the societal perspective			Costs from the household perspective		
	Median	(IQR[a])	%	Median	(IQR[a])	%
Medical costs						
Consultation fees	-		-	170[b]		2
Accommodation cost	2,736	(2,736-2,888)	18	-		
Investigations	2,700	(2,650-2,735)	18	180	(130-215)	2
Medicines						
Amphotericin B	2,160	(1,350-2,970)	14	2,160	(1,350-2,970)	23
Other drugs[c]	174	(109-239)	1	-		
Medical supplies	720	(450-990)	5	-		
Total medical costs	*8,490*		*55*	*2,510*		*27*
Non-medical costs						
Transportation costs	460	(340-660)	3	460	(340-660)	5
Food costs	950	(810-1,240)	6	950	(810-1,240)	10
Total non-medical costs	*1,410*		*9*	*1,410*		*15*
Indirect costs						
Loss of income to the patient	4,400	(1,691-6,555)	29	4,400	(1,691-6,555)	46
Loss of income to the attendant	900	(600-1,305)	5	900	(600-1,305)	10
Monthly interest on loans	200	(95-250)	1	200	(95-250)	2
Total indirect costs	*5,500*		*36*	*5,500*		*59*
Total (rupees)	15,400		100	9,420		100
Total (US$)	355			217		

[a] Interquartile range
[b] Is the same for all
[c] These are miscellaneous drugs such as aspirin, antibiotics,…

The total loss of income to the patient (income loss because of illness and hospitalization) was 4400 rupees, while the income loss for the relative(s) staying permanently with the patient was 900 rupees. School-going patients were absent from school on average 67 days. Households used one or more strategies to cover the costs of treatment: (1) using available cash and savings, (2) taking loans, (3) the sale of assets and/or rental of land and (4) gifts.

Forty-nine per cent of patients covered expenditures by using available cash and savings. However, the amount of money available was insufficient to cover all expenditures and a vast majority of patients (81%) had taken a loan. The median amount borrowed was 4000 rupees

with a reported monthly interest of 5% for most respondents (range 0–10%). The monthly interest payment was 200 rupees. Ninety-one per cent borrowed the money from someone from the same village as the patient, either a neighbour or a moneylender, while 9% got a loan from a friend or a relative. Only five patients (6%) covered all expenditures with available cash and savings. Nine per cent of patients temporarily rented a part of their land in exchange for cash and could regain ownership of their land once they had repaid the loan. One patient sold a parcel of land which resulted in a permanent loss of income. Four per cent sold livestock or poultry while 13% mentioned they would be unable to pay all costs.

Health seeking behaviour and costs prior to the KAMRC

The survey also collected information on household costs and health seeking behaviour prior to admission at the KAMRC (Table 3). Patients visited on average two different providers prior to seeking/receiving care the KAMRC. Only in 24% of cases, these providers suspected/diagnosed the patient to be infected with VL and referred the patient to the KAMRC for specialised treatment. In all other cases, the patient was referred to the centre by either a relative, a member of the same village or the patient knew about the centre him/herself. The total (direct) cost of seeking/receiving care for VL prior to the KAMRC was estimated at 1220 rupees (range 75–10 530 rupees). Medical costs (consultation fees, drugs and tests) constituted 89% and non-medical costs (transportation costs) 11% of total costs.

Table 3: Patients costs and health seeking behaviour prior to the Kala-azar Medican Research Centre

Cost items	Median (INR)	(IQR[a])
Medical costs	1090	(650-2450)
Non-medical costs	120	(620-2300)
Total (rupees)	1220	
Total (US$)	28	

Type of provider consulted	No. of patients	(%)
Private doctor/hospital	49	(64)
Compounder (i.e. quack)	22	(28)
Public health facility	5	(7)
Traditional healer	1	(1)

[a] Interquartile range

DISCUSSION

This study is a first attempt to estimate the direct and indirect costs associated with patient management of VL from a societal and household perspective in Bihar. Data were collected on provider's costs and a structured questionnaire was administered to 77 patients to estimate their direct and indirect costs to receive treatment for VL and was supplemented with information from patient records to improve reliability. The indirect costs were calculated using the human capital method and were reported separately as recommended by the WHO (Tan-Torres Edejer *et al.* 2003).

From our findings, the indirect cost, mainly the loss of income to the patient and relatives, of seeking/receiving care represents the highest cost item. This high indirect cost follows from the long duration of illness and is explained by the fact that patients visited on average two different providers prior to seeking/receiving care at the KAMRC. The importance of indirect costs has been reported in various studies from Africa (Sauerborn *et al.* 1991; Ettling *et al.* 1994).

The results on the health seeking behaviour and the costs incurred by patients prior to the KAMRC should be interpreted with care and should be considered as indicative results rather than robust findings because of recall bias. Nevertheless it shows that a considerable amount of time elapses between the first signs of VL and the time patients receive treatment for VL. Moreover, in only 24% of cases previous providers suspected/diagnosed the patient to be infected with VL and referred the patient to the KAMRC for specialised treatment. Awareness on VL among health professionals should therefore be increased to ensure a fast and accurate diagnosis of VL in the early stage of disease. This will decrease the risk of misdiagnosis and mistreatment and therefore result in a decreased absence from productive activities and reduce the loss of income to the patient.

A few limitations to this study should be mentioned when attempting to generalise our findings. First, the study is based on only one health care facility in an urban centre and costs were collected in a short period of evaluation with a relatively small sample size. The choice of the study site can lead to selection bias as all patients were selected from the same hospital. As a result, the patients described in this study may not be representative for the entire group affected by VL. Although some studies (Desjeux 1996; Guerin *et al.* 2002) suggest an occupational hazard explaining the high number of infected males, there may well be a bias at the level of the household as described by Thakur (2000) where women and young children are not sent to the hospital for care because of the high cost of treatment and the financial burden it

imposes on households. Second, the costs collected at the KAMRC, a charitable hospital, might not be representative for other hospitals in the region or for other regions. The treatment costs in a private clinic (providing health care to an estimated 80% of all detected VL cases in Bihar state) are likely to be substantially higher because actual cost for medications, tubing's, infusions, laboratory investigations and hospital beds will be significantly higher. Similarly, medical care fees like consultation and visiting fees, fees for infusion of the drug will further add to the cost of treatment. An important variable determining costs is the type and duration of treatment and the process of patient management which can be different over hospitals. In this study patients were treated with conventional Amphotericin B deoxycholate where a majority of patients (88%) received infusions on a daily basis and were admitted to the hospital for the full duration of treatment. In other settings, such as in the BPKIHS hospital in Dharan (Nepal), where antimonial treatment is still in use, patients are admitted for the first week and thereafter managed on an outpatient basis (Rijal *et al.* 2003) while in other centres patients are even treated on a complete outpatient basis.

Despite the limitations mentioned above, this study provides valuable information on the total cost of VL and shows that the economic costs related to VL are substantial.

The study shows that patients incur substantial costs to seek and receive treatment for VL. Patients visit several health care providers, receive and pay for inefficient treatments, subsequently depleting the little savings they have, before being diagnosed with VL and receiving appropriate treatment. Most households are forced to take on a loan with high interest rates or sell assets such as livestock to cover the costs of VL treatment. This pattern has also been observed in recent studies on the economic impact of VL in Bangladesh (Ahluwalia *et al.* 2003; Sharma *et al.* 2006) and Nepal (Rijal *et al.* 2006) as well as studies analysing out-of-pocket expenditures and debt in other parts of Asia (Van Damme *et al.* 2004) and in Africa (Sauerborn *et al.* 1996; Mugisha *et al.* 2002). VL leads to catastrophic health expenditures and further impoverishes households but also keeps then into poverty because of the heavy financial commitments on the long term because of indebtedness (Meessen *et al.* 2003).

As VL mainly occurs in poor rural households with weak medical facilities (Bryceson 2001), public health authorities in Bihar should focus on policies that detect VL in the early stage of disease and implement interventions that minimize the burden to households affected by VL. We see a role for the government to ensure access of care for poor patients (Baltussen 2005) because of the high (economic and financial) costs to the patient; we also recommend that public hospitals subsidise treatment of VL to the patient.

More research is required to gain a better understanding of the health seeking behaviour of patients, as well as the socioeconomic impact of VL on households. Globally, despite the development of new drugs such as Paromomycin and Miltefosine, the challenge remains formidable and requires increased and continued investment from the international community to encourage the development of new and improved tools for control of VL, and neglected diseases in general.

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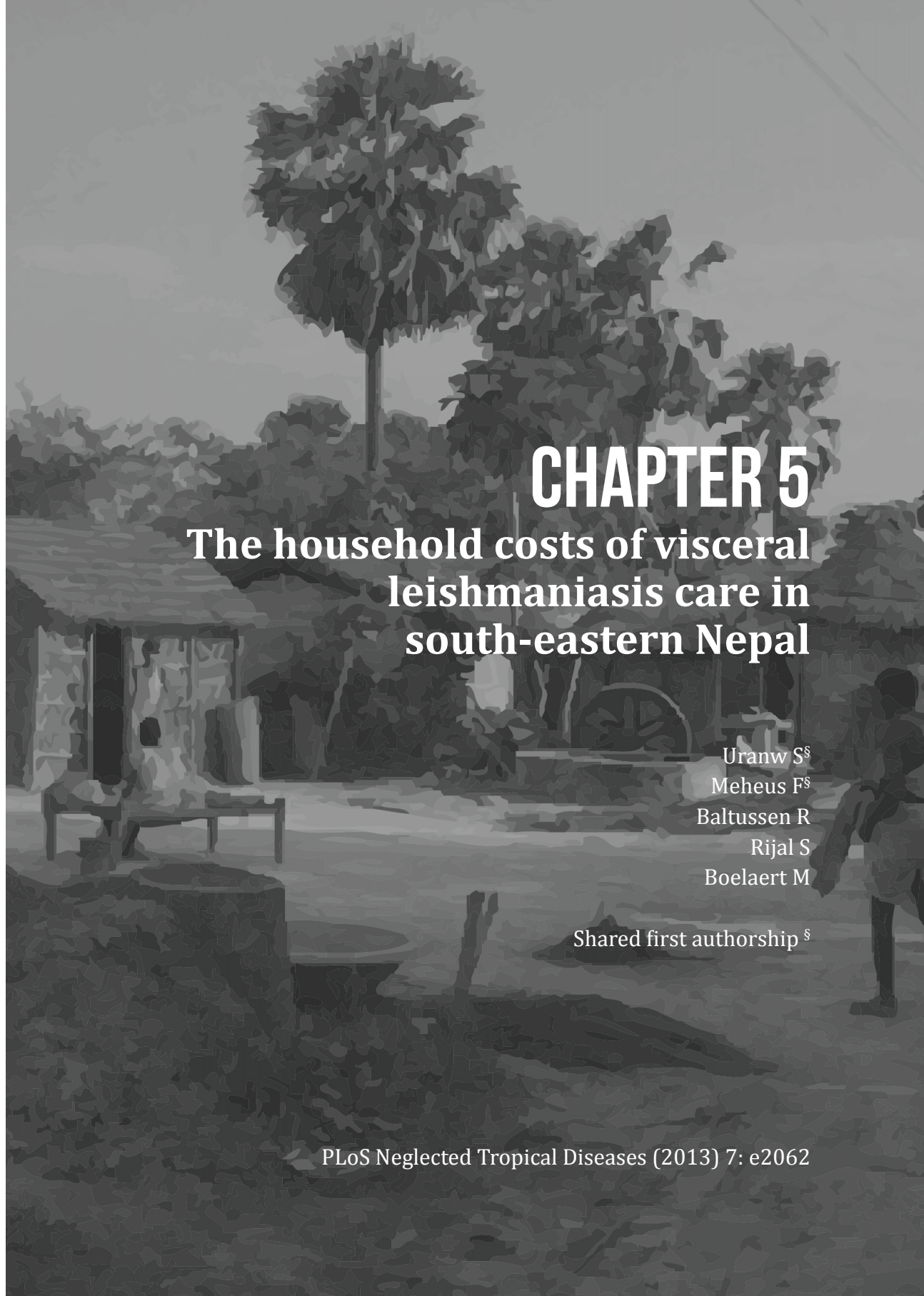

CHAPTER 5

The household costs of visceral leishmaniasis care in south-eastern Nepal

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ABSTRACT

Background and objectives

Visceral leishmaniasis (VL) is an important public health problem in south-eastern Nepal affecting very poor rural communities. Since 2005, Nepal is involved in a regional initiative to eliminate VL. This study assessed the economic impact of VL on households and examined whether the intensified VL control efforts induced by the government resulted in a decrease in household costs.

Methods

Between August and September 2010, a household survey was conducted among 168 patients that had been treated for VL within 12 months prior to the survey in 5 districts in south-eastern Nepal. We collected data on health seeking behaviour, direct and indirect costs and coping strategies.

Results

The median total cost of one episode of VL was US$ 165 or 11% of annual household income. The median delay between the onset of symptoms and presentation to a qualified provider was 25 days. Once the patient presented to a qualified provider, the delay to correct diagnosis was minimal (median 3 days). Direct and indirect costs (income losses) represented 47% and 53% of total costs respectively. Households used multiple strategies to cope with the cost of illness, mainly mobilizing cash/savings (71%) or taking a loan (56%).

Conclusions

The provision of free VL diagnosis and drugs by the Nepalese control programme has been an important policy measure to reduce the cost of VL to households. But despite the free VL drugs, the economic burden is still important for households. More efforts should be put in reducing indirect costs, in particular the length of treatment, and prevent the transmission of VL through vector control.

INTRODUCTION

Since 2005, the Government of Nepal has been involved in a Visceral Leishmaniasis (VL) elimination programme, alongside the governments of India and Bangladesh, to reduce annual VL incidence to less than one case per 10,000 population by 2015 (WHO 2005). VL, also known as kala-azar, is a parasitic disease that is fatal if treatment is not provided timely. The disease is transmitted from humans-to-humans through the bite of a female sandfly.

Geographically, VL occurs in the alluvial plains of the river Ganges, in districts bordering the frontiers between Bangladesh, India and Nepal. The cases in this region account for 60% of the global burden of VL. In Nepal, 8 million people are at risk of acquiring VL in 12 districts in the central and eastern regions of the country (Joshi et al. 2006). Between 2000 and 2010, 17,462 cases and 244 deaths were reported in Nepal although these figures, obtained through passive case surveillance at government health facilities, are likely to be underestimations since many cases are not reported or remain undetected (Epidemiology and Disease Control Division 2010; Singh et al. 2006; Singh et al. 2010).

The cornerstones of the VL elimination initiative are early detection and appropriate treatment, in an attempt to curtail transmission of the disease. A standardized clinical case definition was adopted, the rK39 rapid diagnostic test was introduced to enable faster detection of suspected cases and miltefosine, the first oral drug for VL, replaced sodium stibogluconate (SSG) to which growing failure rates had been reported in Nepal (Rijal et al. 2003). In addition, both VL diagnosis and drugs are now provided free of charge at public health care facilities. These measures along with enhanced vector control resulted in a steady decrease in the annual number of reported VL cases in Nepal from 2,229 in 2003 to 900 in 2010. Another important outcome of the improved case management strategy may be its effect on the household costs of seeking and obtaining appropriate VL care. VL is a disease of poverty affecting the poorest of the poor (Alvar et al. 2006; Boelaert et al. 2009). Households with low incomes and living in precarious housing conditions such as mud -or grass covered houses are most at risk of acquiring VL disease (Singh et al. 2010; Uranw et al. unpublished data). The few studies in Nepal quantifying the economic burden of VL on households and conducted prior to the elimination initiative showed a VL episode to profoundly impact the socio-economic status of the household. Adhikari et al. (2009) reported that up to 26% of previously non-poor households were pushed into poverty as a direct result of out-of-pocket expenditures on VL care while Rijal et al. 2006 showed that the (median) direct and indirect costs of a VL episode were equal to one year of median per capita income. Usually an expenditure exceeding 10% of annual household income is defined as catastrophic, meaning it drives households into destitution (O'Donnell et al. 2008; Ranson

2002). These high costs are caused, amongst others, by long delays, up to 2 months, before correct diagnosis whereby households consulted traditional and private-for-profit providers (Rijal et al. 2006) as well as the long hospitalization due to the use of SSG. Faster screening of suspected cases, enhanced access to free treatment, and a different treatment regimen may reduce these household costs. We examined whether the intensified VL control efforts induced by the elimination initiative resulted in a demonstrable impact at household level in terms of health seeking behaviour, costs and coping strategies.

METHODS

Nepal is administratively divided into 14 zones and 75 districts. In 2010, VL was reported in 12 districts situated in south-eastern Nepal in the Terai region bordering the highly VL-endemic northern state of Bihar in India. The study was conducted between August and September 2010 in five of these highly endemic districts, namely Siraha, Saptari, Sunsari, Morang and Jhapa. VL incidence rates in the study districts varied from 0.52 cases per 10,000 persons per year (Sunsari district) to 2.03 cases per 10,000 persons per year (Saptari district) in 2010 (table 1).

Table 1: Characteristics of districts included in the study

	Siraha	Saptari	Sunsari	Morang	Jhapa
Location	Central Terai	East Terai	East Terai	East Terai	East Terai
Population, 2006	638,375	633,965	710,842	941,614	755,494
VL cases, 2006*	142	255	117	113	52
Case detection rate#	22.2	40.2	16.5	12	6.9
Cases in survey (% of notified cases in 2006)	8 (5.6)	54 (21.2)	12 (10.3)	78 (69.0)	16 (30.8)

Source: National Population & Housing Census 2011; adapted from Mills 1993
*Notified to Epidemiology and Diseases Control Division, Nepal
Number of new cases reported per 100 000 person-years

We searched the medical records of the District Public Health Office in each district and the database of the B.P. Koirala Institute of Health Sciences (BPKIHS) to identify all households in the five districts with a household member treated for kala-azar within 12 months prior to the survey. BPKIHS is a tertiary level hospital situated in Sunsari district and draws many patients from the surrounding areas due to its widespread reputation as a VL treatment and research centre. Patients treated at BPKIHS are not included in the medical records of the District Public Health Office. Furthermore, to minimize recall bias, we only considered the most recent case of VL in the household.

Organization of VL care services

Health care services at the district level are provided by sub-health posts, health posts, primary health care centres and district hospitals (i.e. primary care level) (WHO 2007). A network of female community health volunteers at the village level refer patients to health -and sub-health posts. Patients suspected of VL (defined as individuals with a history of fever of more than 2 weeks with a palpable spleen) seeking care from female community health volunteers, sub-health posts and health posts are referred to primary health care centres or district hospitals for diagnosis by a rapid diagnostic test (rK39 immunochromatographic strip test). If positive, the patient is treated at the PHC or referred to a district hospital (or higher level) if the PHC does not have a medical doctor, which is often observed. All VL drugs are provided free of costs. Diagnosis through parasitology (bone marrow or splenic aspiration) can only be done at district hospitals or above. While private formal providers such as private clinics also provide diagnosis and treatment of VL, free treatment is only available at public facilities. Various anti-leishmanial drugs are available in Nepal: since 2006 SSG, administrated intramuscularly for 30 days, was replaced as first line treatment by miltefosine, an oral drug given for 28 days. Due to its possible teratogenic effect, miltefosine is not given to pregnant women. The second line treatment is amphotericin B deoxycholate given every day for 14 doses.

Data collection & analysis

Information for the study was obtained from patient medical records and a household questionnaire. Medical records at the District Public Health Offices and the BPKIHS were consulted to retrieve data on the type of VL drugs received and the length of treatment. Subsequently households were visited at their homestead by a team of trained field workers who had previously been involved in other kala-azar related community and household surveys in the area. The field workers were supervised on a daily basis by the first author (S. Uranw). They used a pre-tested structured questionnaire administered to the head of the household or the most knowledgeable person. The survey collected data on treatment seeking behaviour (health providers visited, mode of travel, delay to presentation to first qualified health professional, etc.), direct and indirect costs and the coping strategies to meet the health seeking and treatment costs.

Direct medical and non-medical cost data were gathered for each provider visited. Direct medical costs included all out-of-pocket expenditures by the household on consultation, medicines and laboratory tests. Direct non-medical costs included expenditure on transportation to and from the health facility, food costs and other daily expenditures for the patient and accompanying family members. The indirect cost of a VL episode represented the loss of productivity within the household due to illness and was estimated using the human capital approach. The loss of

productivity was valued in terms of the loss of earnings of the patient and household members caring for the patient (either at home or hospital). For patients and attendants, the daily wage rate was estimated and multiplied by the number of work days lost to obtain the indirect cost of a VL episode. The daily wage rate was determined by asking a series of questions on the daily monetary income (the main source of income to most household members was daily labour). For patients and attendants reporting farming as their main source of income, the survey collected data on the yearly production of each produce which was then valued with local market prices and divided by the number of agriculturally active household members. We also estimated total household income as the sum of monthly cash income from daily labour for each economically active household member, the income from agriculture, income from sales of animals and animal products (e.g. milk) and remittances from family members.

Analysis

The data is described using descriptive statistics showing proportions, means and standard deviations. We also presented medians and interquartile ranges (25^{th} and 75^{th} percentile) because of skewed distributions in the cost data; many households reported zero out-of-pocket expenditure for some cost categories and providers, in particular informal health care providers. Costs were defined as catastrophic if they exceeded 10% of annual household income (O'Donnell et al. 2008; Ranson 2002). All costs were converted from Nepalese rupees (Rs.) to US dollars using the exchange rate prevailing at the time of the study (1 USD = Rs. 74.8; OANDA August 2010). Data entry and cleaning were done in Microsoft Excel and analysis in STATA v10.1 (Stata Corp., College Station Tx, USA).

Ethical considerations

Ethical clearance was obtained from the ethics committee of the BP. Koirala Institute of Health Sciences, Nepal and the ethics committee of the University of Antwerp, Belgium. Patient's medical records were reviewed retrospectively and all information retrieved from medical records was anonymized. Signed informed consent was obtained from all adult patients and from a parent or guardian of participating minors. All households that were approached for the study, whether they accepted to participate or not, received a free long-lasting insecticide treated net (Vestergaard Frandsen A/S, Denmark) as a compensation for their time spent with the survey team.

RESULTS

Characteristics of study participants and the household

We randomly retrieved a total of 200 households where a case of VL occurred in the past 12 months in the five districts, of which 168 households were located by field workers and accepted to be interviewed. The majority of patients were male (60%) and 41 of them were head of the household (24%). Most patients were over 14 years of age (68%); the median age was 19 (IQR 12.5-35). Male patients were significantly older than female (median age 22.5 versus 17.0; $p < 0.05$). The percentage of women of childbearing age (15-49 years) among patients was 19%. The median household size was 5.7 persons.

Out of 168 patients, sixty-one (36%) were economically active at the time of illness, most of them day labourers (80%) such as rickshaw driver or farm labourers. Few patients were engaged in small-scale farming (n=5; 8%) or were salaried workers (n=4; 6%). The median monthly income of an economically active patient (n=60) was Rs. 6,000 or 81 US$ (range 27-162 US$). The median monthly income of the household (n=168) was Rs. 10,243 or 138 US$ (range 87-163 US$) giving a median per capita monthly income of Rs. 1,882 or 25 US$ (range 20-30 US$).

The vast majority of households lived in non-permanent housing structures either consisting entirely of natural materials (49%) or a combination, usually mud walls and metal sheets as roof (45%). Eighteen per cent of households owned land (n=30); 27 of these households cultivated some crops on their land, mainly paddy rice and wheat. Most households also owned some livestock (83%), usually goats (56% of households; median 3 heads), cows (44%, median 2.5) or chickens (36%, median 5). Fifty-eight per cent of households owned a bicycle, 56% a mobile phone and 36% a radio.

Health-seeking behaviour

Patients visited a median of 2 health providers including the one who eventually treated them (IQR 1-2) (table 2). For 91 households (55%), a public provider was the patient's first point of contact; other households first visited a private (qualified) provider (n=34; 20%), a traditional healer (n=26; 15%) or a chemist or pharmacy (n=16; 10%). The main reasons behind the choice of the first provider were proximity (49%) and the perceived (good) reputation of the health provider (38%). Traditional healers were chosen for their proximity, public providers (health centre or hospital) most often for their reputation while for private providers it was a mix of both. Ninety patients (54%) were submitted to a VL diagnostic test on their first visit but this varied considerably by type of provider: all patients presenting at public hospitals were

tested for VL, compared to 56% at public health centres and 39% at private providers. Of the patients that did not receive a VL diagnostic test at a public health centre or a private provider on their first visit, respectively 60% and 55% were subsequently referred by the provider to a public hospital for testing and treatment. Households that used the services of an unqualified provider first, were more likely to visit either another unqualified provider or a private provider afterwards. Approximately 21% (n=35) of households visited three different providers; 4% (n=7) of households visited 4 different types of health providers.

The median delay between the onset of symptoms and presentation to a qualified health provider (i.e. patient delay) was 25 days (IQR 20-30). Once the patient had presented to a qualified provider, the median delay to correct diagnosis of VL was 3 days (IQR 2-7). The total median delay from onset of symptoms to start of treatment was 31 days (IQR 23-35). While none of the delays varied with age or gender, there was a significant and positive relationship between the total delay and the number of providers visited (p<0. 01).

Treatment regimens

The vast majority of patients in our study were treated with either miltefosine (83%) or conventional amphotericin B (15%) in case of relapse as recommended by the 2005 guidelines of the VL elimination initiative (WHO 2005). Four patients were treated with SSG (2%), two of them by a public provider. The other two patients treated with SSG by a private provider were unexpected in our survey because these patients are usually not included in the DPHO records. In addition, both patients reported not to have paid for the SSG drugs. Upon closer inspection, these patients were from the same village in Morang district on the border with Bihar state (India). After discussion with the local vector control officer, they had probably obtained the SSG free of charge from a private charitable hospital in Bihar and subsequently received the injections at a health facility in Nepal by trained health workers.

Direct costs

The average and median direct household costs incurred by type of provider are given in table 3. All but three patients received VL treatment at a public hospital, the remaining 3 patients were treated at a public health centre (n=1) or a private qualified provider (n=2).

The median direct cost of an episode of VL across all providers was Rs. 4,905 (IQR 3,025-7,125) or US$ 66 (IQR 41-96). Direct medical costs were Rs. 2,390 (IQR 1,100-4,290) and non-medical costs Rs. 2,300 (IQR 1,550-3,350) or 51% and 49% respectively of total median direct costs. Direct medical costs arose from expenditures on consultation fees, miscellaneous drugs and laboratory investigations (including diagnostic tests). The survey confirmed that none of the

Table 2: Health seeking behaviour of households (n=168)

Variable	N° (%) of patients
Type of health provider first visited	
Traditional	26 (15.5)
Chemist or pharmacy	16 (9.5)
Village health worker	6 (3.6)
Public, primary	23 (13.7)
Public, hospital	63 (37.5)
Private doctor/clinic	34 (20.2)
Delay to presentation (in days) (median; IQR)	25 (20-30)
Delay to diagnosis (in days) (median; IQR)	3 (2-7)
Number of health providers visited	
1	63 (37.5)
2	70 (41.6)
3	28 (16.7)
4	7 (4.2)
Diagnosed with VL at first visit?	
Yes	90 (53.6)
No	78 (46.4)
Mode of transportation to first facility	
Foot	38 (22.6)
Bicycle	28 (16.7)
Bus	96 (57.1)
Other	6 (3.6)
Mode of transportation to treatment facility[1]	
Foot	4 (2.4)
Bicycle	10 (6.0)
Motorbike	2 (1.2)
Bus	148 (88.6)
Other	3 (1.8)
Distance between home and treatment facility (kilometers)	
< 20	45 (26.8)
20-60	86 (51.2)
> 60	37 (22.0)

[1] The treatment facility is the health provider where the patient received VL treatment. In 98% of cases this was a public hospital.

households had to pay for VL drugs. Median direct medical costs were highest for households visiting private providers (median Rs. 2000; IQR 1,475-3,575), in particular payments for ancillary drugs (e.g. antibiotics, antipyretics or vitamin injections). The direct non-medical costs, consisting of transportation, food and other expenses (i.e. small daily expenses) were highest at the public hospital. The high food costs at public hospitals (median: Rs. 1,400; IQR 700-2,000) arose from the hospitalization of the patient and accompanying family member(s) for VL treatment. The median duration of hospitalisation was 10 days (IQR 7-16) and was the same for patients receiving SSG or miltefosine but higher for patients treated with conventional amphotericin B (median: 14 days; IQR 8-20). Direct (medical and non-medical) costs did not vary by gender or income quintiles, but direct medical costs increased with the patient's age.

Indirect costs

VL is a syndrome characterized by prolonged fever, weight loss, anaemia, fatigue and enlargement of the liver and spleen. As a result patients are either severely limited or not able at all to carry out their daily activities and need much support from family members. Among the 168 patients, 95% (n=160) reported that VL illness had a severe impact on their normal functioning and resulted in a loss of income to the household, either wage losses to the patient or caretakers, losses in agricultural output or other earnings. Patients reported not being able to carry out their normal daily activities for a median number of 57 days (IQR 51-65) (table 4). As a result the median loss of income was Rs. 12,400 for economically active patients. Since only 36% of patients were economically active, the value of time lost across all patients, both the economically active and non-active, was on average Rs. 4,731.

Patients were attended by on average 1.1 household members (range: 1-2). These caretakers reported a median loss of 15 workdays (IQR 10-30) mainly due to accompanying the patient to the various health providers and staying with him/her for the full duration of hospitalization. The median loss of income to caretakers was Rs. 2,583 (on average Rs. 2,279 across all caretakers). The median total value of time lost to the household per episode of VL was Rs. 4,500 (IQR 1,500-12,167).

Table 3: Direct medical and non-medical costs of treatment per patient by type of provider (Rs. 2010)

	Traditional (n=28)		Chemist/pharmacy (n=25)		Village health worker (n=6)	
	Mean (sd)	Median (IQR 25-75)	Mean (sd)	Median (IQR 25-75)	Mean (sd)	Median (IQR 25-75)
Direct medical costs						
Consultation	210 (363)	50 (0-200)	74 (76)	50 (10-100)	72 (114)	30 (10-60)
Ancillary drugs	425 (847)	0 (0-750)	1,242 (1,526)	700 (500-1,400)	657 (242)	670 (500-800)
Laboratory investigations	45 (137)	0 (0-0)	225 (218)	100 (0-400)	67 (103)	0 (0-200)
Total direct *medical* costs	679 (973)	300 (0-1,000)	2,034 (2,950)	1,150 (500-2,000)	795 (325)	785 (650-1,000)
Direct non-medical costs						
Transportation	7 (30)	0 (0-0)	113 (194)	0 (0-100)	0 (0)	0 (0-0)
Food	314 (567)	0 (0-350)	107 (149)	0 (0-200)	17 (26)	0 (0-50)
Other	0 (0)	0 (0-0)	2 (10)	0 (0-0)	8 (20)	0 (0-0)
Total direct *non-medical* costs	321 (564)	0 (0-350)	222 (319)	100 (0-200)	25 (42)	0 (0-50)
Total direct costs	1,001 (1,150)	775 (75-1,700)	2,256 (3,158)	1,150 (500-2,200)	820 (350)	785 (700-1,000)

Table 3: Continued

	Public, primary (n=32)				Public, hospital (n=165)				Private doctor/clinic (n=52)			
	Mean	**(sd)**	**Median**	**(IQR 25-75)**	**Mean**	**(sd)**	**Median**	**(IQR 25-75)**	**Mean**	**(sd)**	**Median**	**(IQR 25-75)**
Direct medical costs												
Consultation	56	(85)	25	(10-50)	79	(191)	50	(25-70)	222	(155)	200	(200-250)
Ancillary drugs	1,002	(845)	600	(500-1,345)	1,120	(1,580)	650	(400-1,080)	1,714	(1,567)	1,200	(825-2,000)
Laboratory investigations	317	(349)	200	(95-425)	442	(603)	300	(200-500)	748	(767)	500	(300-875)
Total direct *medical* costs	1,375	(1,107)	975	(608-1,900)	1,550	(1,703)	1,000	(720-1,688)	2,684	(2,038)	2,000	(1,475-3,575)
Direct non-medical costs												
Transportation	75	(114)	23	(0-100)	431	(343)	450	(200-500)	390	(392)	300	(150-500)
Food	123	(144)	100	(0-200)	1,424	(968)	1,400	(700-2,000)	414	(571)	200	(100-500)
Other	29	(97)	0	(0-0)	239	(216)	200	(100-400)	68	(183)	0	(0-0)
Total direct *non-medical* costs	226	(290)	125	(23-275)	2,090	(1,207)	2,000	(1,300-2,700)	882	(1,007)	600	(300-1,100)
Total direct costs	1,601	(1,266)	1,075	(693-2,260)	3,640	(2,531)	3,130	(2,135-4,223)	3,582	(2,545)	2,500	(2,000-5,000)

	Total costs all providers			
	Mean	**(sd)**	**Median**	**(IQR 25-75)**
Direct medical costs				
Consultation	203	(297)	88	(40-270)
Ancillary drugs	2,134	(2,137)	1,500	(700-2,850)
Laboratory investigations	786	(872)	600	(300-1,000)
Total direct *medical* costs	3,123	(2,745)	2,390	(1,100-4,290)
Direct non-medical costs				
Transportation	574	(481)	500	(300-800)
Food	1,619	(1,018)	1,500	(1,000-2,250)
Other	260	(252)	200	(100-480)
Total direct *non-medical* costs	2,453	(1,400)	2,300	(1,550-3,350)
Total direct costs	5,576	(3,552)	4,905	(3,025-7,125)

Table 4: Indirect costs (Rs. 2010)

	Mean	(sd)	Median	(IQR 25-75)
Patients' duration of illness (days)§	60	(18)	57	(51-65)
Number of attendants per patient	1.1	(0.3)	1.0	(1.0-1.0)
Workdays lost by attendants	21	(16)	15	(10-30)
Loss of income; working patients only (n=61)	13,030	(5,638)	12,400	(9,800-15,400)
Loss of income; all patients (n=168)	4,731	(7,136)	0	(0-10,700)
Loss of income working attendants only (n=134)	3,112	(2,300)	2,583	(1,500-4,000)
Loss of income; all attendants (n=183)	2,279	(2,404)	1,500	(0-3,100)
Total loss of income to the household£	*7,213*	*(7,217)*	*4,500*	*(1,500-12,167)*
Total payment on loan*	2,611	(2,176)	2,080	(1000-3,300)
Total indirect cost	8,084	(7,391)	5,167	(3,000-13,290)

§ Consists of the various types of delays plus the treatment duration
£ Across all patients & attendants
* For those with interest payments

Coping strategies

Households used a number of strategies to cope with the costs of VL illness. Many of these strategies resulted in additional costs to the household; e.g. in terms of interest payments on loans or hiring labour to replace the sick household member. The survey identified three strategies to cope with the financial costs of VL illness: mobilizing cash/savings, taking a loan and sales of livestock. Mobilizing cash or savings was the most frequent coping strategy. Seventy-one per cent (n=120) of households used their savings to pay for health care expenditures, although for 54% of these households it was not enough to cover all medical costs. Out of those 120 households, 75% (n=90) of households reported that the savings were supposed to buy food, in other cases assets (n=30). Fifty-six per cent (n=94) of households took a loan to finance the costs of care, most often from a member of the same village (71%), followed by friends or peers (17%) or an informal money lender (6%). When borrowing from friends, the loan was interest free. In other cases (n=57), the amount to be repaid was on average 140% the original amount borrowed, usually through monthly instalments. A collateral was not often provided for the loan: four households provided assets as collateral, one household that took a loan from a bank provided their house. Seventeen per cent of households sold livestock to cover the costs of care (n=29). Forty-two per cent of households chose more than one strategy (n=71), mainly using cash/savings and a loan (n=47), while 2% (n=4) had to revert to all three strategies to cope with the costs of VL illness.

Households also used various strategies to compensate the labour lost due to VL illness. Nine households hired external labour to replace either the patient or caretakers in the field at a rate of Rs. 200 per day for a median of 60 days (IQR 60-60). Twenty-three per cent of patients were replaced by a family member that was a school-going child for the duration of their illness (n=14).

Table 5: Summary of direct and indirect costs per VL episode (Rs. and in US$ 2010)

Item	Mean		Median	
	Rs.	US$	Rs.	US$
Direct and indirect costs				
Direct medical cost	3,116	42.2	2,385	32.3
Direct non-medical costs	2,444	33.1	2,297	31.1
Indirect cost	8,084	110.7	5,167	70.8
Total household costs	13,659	187.1	12,050	165.1
Annual income				
Household	127,074	1,720.7	122,665	1,661.0
Per capita	23,366	316.4	22,539	305.2
Median costs as a % of				
Annual household income			11%	
Annual per capita income			57%	

Exchange rate 1 US$=74 Rs. (Sept. 2010)

DISCUSSION

During the past five years, considerable efforts were made by public health authorities in Nepal towards the elimination of VL such as the decentralisation and provision of free diagnosis and treatment and the introduction of the oral drug miltefosine in the public health system. In this study we studied the health seeking behaviour and documented household costs and coping strategies for one episode of VL from the perspective of the patient in a miltefosine-based treatment program. From our findings, the following observations can be made.

First, our results showed that the cost of a VL episode to patients and their family was high notwithstanding the free provision of drugs and diagnostics by the government. With a median total cost of US$ 165 per episode, the economic burden of VL across all households was 11% of annual household income or 57% of median annual per capita income. This cost included

both direct costs (medical and non-medical out-of-pocket expenditures) and indirect costs (productive time losses due to illness). While about half (51%) of the households exceeded the catastrophic threshold of 10% of annual household income, it would be wrong to conclude that the economic consequences of VL illness were not significant for the other households. Because VL is a disease of poverty primarily affecting the poorest income groups (Boelaert et al., the ability to cope with the costs of VL illness are limited. This was evident from the coping strategies households used whereby a majority of households were forced to take a loan to pay for the costs of care and/or use all their savings. However, without the free provision of VL drugs the median cost of an episode of VL would be US$ 226 and the proportion of households exceeding the catastrophic threshold would increase from 51% to 74% (assuming a drug cost of US$63 for a 28-days course of miltefosine at WHO preferential prices (Olliaro & Sundar 2009)).

Secondly, direct costs accounted for 47% of total costs and were largely caused by out-of-pocket expenditures households made on ancillary drugs and food. Households that visited private-for-profit health providers incurred substantial expenditures on ancillary drugs. These ancillary drugs, most frequently antibiotics, antipyretics or vitamin injections, were given to patients prior to their referral to a public hospital for VL treatment. From our study we cannot say whether the prescription of these ancillary drugs were justified on medical grounds. Besides the ancillary drugs, another important direct cost component were the high food costs for the patient and accompanying relatives and was caused by the extensive stay at the hospital for treatment. Although miltefosine is an oral drug, patients stayed at the hospital for a median of 10 days.

A number of studies had been carried out prior to the VL elimination initiative (Rijal et al. 2006; Adhikari & Maskay 2005; Adhikari et al. 2009). Our findings seem to suggest that, compared to these studies, the economic burden of VL (as a % of household income) has decreased. In particular the magnitude of indirect costs (as a % of total costs) was less in our study likely due to a shorter patient delay. We cannot say whether the shorter patient delay observed in this study was the result of increased patient knowledge of VL, but the previous studies reported that traditional providers were most commonly the patient's first choice of provider, which may have lengthened the delay until VL diagnosis. However, these conclusions need to be considered as tentative. For instance the total cost of VL in our study was higher compared to Rijal et al. (2006) but much lower compared to Adhikari & Maskay (2005) and Adhikari et al. (2009) while the household income of VL affected households in our study was higher compared to all three studies (to enable comparisons the cost data in these articles were adjusted to the year 2010 using the consumer price index (World Bank 2012)). While

daily wages in Nepal have increased over the years, partly to compensate for the high inflation rate, methodological differences between the studies and in particular the small sample sizes of the first two studies (respectively 18 and 7 households) limit their generalizability beyond the communities or villages where these studies were carried out.

Despite the provision of free VL drugs, we have shown that households still incurred substantial medical out-of-pocket expenditures, especially at private providers. It remains to be seen, however, if these medical costs can be prevented or at least diminished. While prepayment schemes, such as community-based health insurance, may be a solution, coverage in Nepal is very low and expansion of coverage to VL affected households is unlikely in the near future. More realistic and feasible approaches consist of reducing indirect costs and vector control. Treatment duration can be reduced substantially by considering alternative VL drugs to miltefosine as single-dose liposomal amphotericin B or a short course combination therapy Meheus et al. 2010). Vector control, such as indoor residual spraying, has been shown to be effective in reducing the number of sandflies inside the house (Chowdhury et al. 2011a; Chowdhury et al. 2011b) and may therefore reduce disease transmission. Since 2011, the Government of Nepal has also introduced a conditional cash transfer programme whereby households receive Rs. 1,000 (US$13.5) upon completion of treatment at a public hospital (Adhikari et al. 2011). This payment can be used to cover transportation costs but was not yet in place when we carried out the household survey. However from our study, the total transportation costs of households were smaller than Rs. 1,000 while food costs were higher. The conditional cash programme therefore ought to be expanded to include food costs as well.

This study had a number of limitations. Because patients were selected from the medical records of the District Public Health Offices and the BPKIHS, only patients treated at public health facilities were included in the study. The records kept by the District Public Health Offices are obtained through passive surveillance from cases detected and treated by public health facilities. Private for-profit providers are not required to report patients treated at their facilities. Due to the low incidence of VL and the high number of private practioners in Nepal, it would have been difficult and costly to find and interview these patients. Because patients exclusively treated at private-for-profit providers were excluded, we probably underestimated the true burden of VL. Despite this limitation, our findings were still representative for a large proportion of the VL population because in Nepal, contrary to India, a relatively small proportion of patients seek VL treatment from private-for-profit providers (about 11% of patients according to (Mondal et al. 2009). Nonetheless, efforts should be made in the future to include the private sector in the control of VL.

A second limitation is related to the recall bias. With decreasing VL incidence rates in Nepal, we have chosen a recall of 12 months to allow the identification of a sufficient number of households. To minimize the recall bias we only analysed the most recent case of VL in the household. Because of the clustering of VL in communities and villages, several cases of VL often occur in the same household. For instance, in 44% of households in our study one or more members had been treated for VL before, often within a few years. The occurrence of more than one case of VL in the same household would significantly increase the economic impact of VL to households. And even if these cases do not occur in the same year, the risk of impoverishment and indebtedness would still be much higher.

CONCLUSION

With a shorter delay to diagnosis once the patient has presented to a qualified health provider and the free provision of the correct first-line drug, our study indicates that the case management component of the Nepalese VL programme performs rather well. In particular free VL diagnosis and drugs at public health facilities have been an important policy measure in Nepal to lower financial barriers and improve access to VL diagnosis and care. Without this policy the economic burden of VL would have been much higher. However, the economic impact of VL is still considerable and intensified efforts are needed to further reduce the burden of VL to affected households or prevent the transmission of VL. These include shortening the duration of stay at the hospital and expanding demand side financing mechanisms to cover a wider range of costs incurred by households.

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CHAPTER 6

The economic burden of visceral leishmaniasis in Sudan: an assessment of provider and household costs

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ABSTRACT

Visceral leishmaniasis (VL) is a neglected parasitic disease that is fatal if left untreated and is endemic in eastern Sudan. We estimated the direct and indirect costs of treatment for VL from the perspective of the provider and the household at three public hospitals in Gedaref State. The median total cost for one VL episode was estimated to be US$ 450. Despite the free provision of VL drugs at public hospitals, households bore 53% of the total cost of VL with one episode of VL representing 40% of the annual household income. More than 75% of households incurred catastrophic out-of-pocket expenditures. The length of treatment of 30 days led to important costs for both health providers and households. Alternative treatment regimens that reduce the duration of treatment are urgently needed.

INTRODUCTION

Visceral leishmaniasis (VL) is a neglected parasitic disease endemic in many parts of East Africa in particular in eastern Sudan with important foci also found in South Sudan, Ethiopia, Kenya and Uganda. VL is caused by *Leishmania donovani* and transmitted to humans through the bite of a female phlebotomine sandfly. The disease, also known as kala-azar, is systemic and results in the death of the infected individual if treatment is not provided in time. Signs and symptoms of VL include prolonged fever, fatigue and weakness, anaemia and enlarged lymph nodes, spleen and liver (Murray *et al.* 2005)

The public health importance of VL in East Africa is undervalued not least because of the limited knowledge on the disease burden, including the socio-economic aspects of the disease. In the Indian subcontinent (India, Nepal & Bangladesh) studies examining the financial and economic burden of VL have led to a better understanding of the impact and the financial consequences of VL illness at the individual and household level (Meheus *et al.* 2006; Sharma *et al.* 2006; Uranw *et al.* 2013). Other tropical neglected diseases, in particular the helminthic infections, have been successful in garnering international attention and funding by demonstrating the low cost of control interventions and their cost-effectiveness. However, to date, no studies on the costs of VL illness, either from the household or the health-care provider perspective, have been carried out in East Africa. Better cost data would allow the use of economic evaluation as a tool to inform policy decisions and could help to make the case for increased investment and resource allocation in VL control policies and programmes.

Therefore we carried out a costing study on VL in Gedaref State in eastern Sudan. The aim of this study was to estimate both the cost of providing VL diagnosis and treatment services (i.e. health-care provider perspective) as well as the cost to patients and their family to access these services (i.e. household perspective).

MATERIALS AND METHODS

This study is part of a research project on the cost-effectiveness of treatment alternatives for VL in Sudan initiated by the Leishmaniasis East Africa Platform (LEAP) and the Drugs for Neglected Diseases Initiative (DND*i*).

Study sites

The study was conducted in Gedaref State, Sudan[1] between October 2009 and May 2011. Gedaref State is located in eastern Sudan bordering Ethiopia and had an estimated population of 1.35 million in 2008, representing 3.4% of the Sudanese population (Central Bureau of Statistics Sudan). Agriculture is the main economic activity in the State with main products including sorghum, sesame, millet and peanuts. Gedaref State is the main VL endemic area in the country and recently experienced an important increase in the number of reported VL cases (deaths) from 2,792 (109) in 2006 to 5,050 (142) in 2010 (Gedaref State Ministry of Health, unpublished data). However, because many people do not have access to health services, the true incidence and mortality of VL are probably much higher Collin *et al.* 2006). It is estimated that about 20,000 VL cases occur annually in Sudan. The number of cases is expected to rise because of migration into endemic areas, climate change, HIV/VL co-infection and the overall lack of efforts to control the disease (Desjeux 1996).

The public health care system in Sudan is organized across three levels: the Federal Ministry of Health (FMOH), the State Ministries of Health (SMOH) and the district level. The delivery of health care also follows a three-tiered structure. Primary health care units are the lowest tier followed by health centres and then rural/community hospitals (WHO Regional Office for the Eastern Mediterranean 2006). The National Malaria, Schistosomiasis and Leishmaniasis Administration (NMSLA) of the FMOH is responsible for VL control activities in Sudan. Currently, VL control activities consist only of passive case detection and treatment at rural/community hospitals. Due to the low level of human and financial resources, VL treatment services are often provided in collaboration with private-not-for-profit partners, either through existing health facilities (e.g. Kassab hospital supported by the Institute of Endemic Diseases (IEND) and DND*i*) or by establishing independent health facilities (e.g. Um-el-Kher hospital used to be operated by Médecins sans Frontières (MSF) and now by the Ministry of Health). Although there are no routine VL prevention activities, MSF has been involved in the distribution of bednets in endemic areas since 1995 (Malaria Consortium 2010; Ritmeijer *et al.* 2007).

We purposefully selected 3 health facilities in Gedaref State as study sites: a public rural hospital located in Doka, the State's second largest city; a rural hospital in Kassab and a hospital in Bazora town. The hospital in Doka, funded by the Ministry of Health (MoH), is the largest of the three facilities and has a capacity of 82 beds. It is a referral hospital providing a wide range of medical services including surgery and obstetrical services. Kassab hospital has a capacity of 68 beds and receives funding from both the MoH and DND*i*. This hospital, located

[1] Sudan here refers to North Sudan and excludes the Republic of South Sudan that became an independent State in 2011.

between Doka and the State capital Gedaref, mainly provides VL treatment services. Both Doka and Kassab hospital cover the area between Rahad and Atbara rivers together with other rural hospitals in the same area. Bazora hospital is the smallest of the three facilities with a capacity of 51 beds and covers the Rahad river basin area. It is operated by the MoH and also receives funds from the World Health Organization.

Current VL case management in Sudan

Sodium stibogluconate (SSG), a pentavalent antimony compound, is the first-line treatment for VL in Sudan (Federal Ministry of Health Sudan 2004) and is administered intramuscularly on a daily basis for 30 days at a dosage of 20 mg per kg per day. Although widespread resistance to SSG has been reported in the Indian subcontinent (Rijal *et al.* 2003; Sundar *et al.* 2000), the drug is still effective in Sudan with a cure rate of 92% (Hailu *et al.* 2010; Melaku *et al.* 2007; Musa *et al.* 2012) but has numerous side-effects including nausea, diarrhoea, muscle pains, arrhythmia and pancreatitis. Other treatment options are currently being evaluated (Omollo *et al.* 2011). Diagnosis of VL is made with either the rK39 rapid diagnostic dipstick test, the Direct Agglutination Test (DAT) and/or microscopic confirmation of the parasite in lymph node or bone marrow aspirate (Zijlstra *et al.* 1992*; Zijlstra et al.* 2001). Both diagnosis and treatment for VL are provided free of charge at public facilities. Other medical and non-medical costs (registration fee, laboratory investigations, food) need to be paid out-of-pocket by the patient. All patients diagnosed with VL are admitted for the full duration of treatment to ensure 100% adherence and to monitor for side-effects because patients are usually high-risk presenting with severe anaemia and malnutrition (Collin *et al.* 2004).

Costing methodology

The costs of VL were assessed from the perspective of the health-care provider as well as the household. Each perspective involved a different methodology and data collection process described in more detail below (table 1).

Table 1: Overview of costing methods used to estimate the unit cost of VL care and household costs in Sudan (2010) for one VL episode

	Perspective			
	Provider		**Household**	
Costs included	Direct medical costs of VL treatment (drugs, lab. tests)[1]	Other recurrent and capital costs	Direct medical (registration, drugs, lab. test) and non-medical costs (food, transportation[1]	Indirect costs, i.e. productive time losses
Estimation method	Ingredient approach	Step-down costing	-	Human capital method
Data sources	Review of 250 medical records of VL patients	Health facility records and primary data collection	Questionnaire[3]	Questionnaire[3]
Intermediary outcome	Median medical cost per patient (a)	"Hotel" unit cost per inpatient day (b)	Median out-of-pocket expenditures on VL services (c)	Median loss of income to the patient and family members caring for the patient (d)
	(a)+[(b) x ALOS[4]] = Median cost of VL care per VL episode		(b)+(d)= Median cost incurred by households per VL episode	
	Median cost per episode of VL			

[1] Medical goods and services charged to patients were excluded to avoid double counting with the analysis from the household perspective;
[2] Detailed medical records were only available at Kassab hospital. Calculations on direct medical costs of VL treatment were only done at this hospital and assumed to be the same for the other 2 hospitals.
[3] Data from the household perspective was collected from Kassab and Bazora hospital. There were no patients attending Doka hospital at the time of the study due to a shortage of SSG.
[4] ALOS = average length of stay

Costs from the provider perspective

The aim of the analysis from the providers' perspective was to estimate the cost of inpatient care at the health facilities included in the study to provide VL treatment for one episode of VL. We only considered the cost of inpatient care since patients are hospitalized for the full duration of treatment and are not managed on an outpatient basis. Because of data constraints we faced at the health facilities, we estimated the medical costs of VL care (drugs, diagnosis,

medical supplies, laboratory investigations) separately from the cost of hospitalization by combining step-down cost accounting with an ingredients approach. These methods have been frequently employed in similar studies in Africa (e.g. Hansen *et al.* 2000; McPake *et al.* 2011; Van der Plaetse *et al.* 2005). Cost estimations represented economic costs whereby all goods and services were valued including voluntary labour and donated or subsidized goods and services (Creese & Parker 1994). All data was collected for the year 2008.

The medical cost of VL care was calculated using the *ingredients approach*, whereby the quantity of inputs used were multiplied by their price, with data obtained from a random retrospective sample of 250 medical records of patients that attended Kassab hospital in 2008. We retrieved information on demographic characteristics, the date of admission and discharge, and the amount of SSG, laboratory investigations and medical supplies patients received. This estimation was only done at Kassab hospital for lack of sufficiently detailed medical records at the other two facilities. The price of generic SSG (Albert David, India) was US$ 8.25 per 30ml vial of 100mg/ml (WHO 2010). The unit costs of VL diagnosis and other laboratory investigations were also estimated using an ingredients approach by observing resource utilisation at the laboratory of Kassab hospital. The prices of medical and laboratory supplies and equipment were obtained from specialized suppliers in Khartoum. All items paid for by the patient were excluded from this analysis to avoid double counting with the data collected from the household perspective.

The *step-down costing* was used to allocate recurrent non-medical and capital costs and calculate the unit cost per inpatient day. This unit cost corresponded to the WHO definition of a "hotel" unit cost, which excluded the medical costs of VL care estimated with the ingredients approach described above (WHO-CHOICE 2012). At each facility, information on *recurrent expenditures* were obtained from the financial records and consisted of aggregated data on administration costs (printing, stationary), vehicle running costs (fuel, maintenance), maintenance of buildings, utilities (electricity and water), etc. Personnel costs were not included in the financial statements and were estimated by compiling a list by department/unit of all staff by type and grade with their monthly salary and allowances. Staff that worked on a voluntary basis or were paid by external partners were given the same salary as personnel of the same type and grade according to government salary scales.

Capital costs included buildings, equipment, vehicles and furniture. An inventory list of equipments and furniture as well as the size of buildings was established for all departments/units. Capital items were valued at replacement cost: the price of equipment, furniture and vehicles was obtained from local suppliers (market prices) while the replacement cost of

buildings was based on the rental price per square meter of office space in the area. Capital costs were annualized using a discount rate of 10% which is the rate mostly used for project appraisals in Africa. A discount rate of 0% (i.e. straight-line depreciation) and standard rates of 3% and 5% (Drummond *et al.* 2005; Gold *et al.* 1996) were used in the sensitivity analysis. We assumed a lifespan of 30 years for buildings, 10 years for equipment and furniture and 5 years for vehicles.

The *step-down costing* was applied as described by Conteh & Walker (2004) using an adapted version of the WHO-CHOICE2 CostIt software package for estimating hospital unit costs. Briefly described, the various departments/units at each health facility were divided into direct and indirect cost centres. Direct costs centres provided services directly to the patient (e.g. outpatient unit or wards), while indirect cost centres provided general services that are necessary to run a hospital, but were not directly related to patient care such as the administration or maintenance department. The final (direct) cost centre of interest to this study was the inpatient ward (all wards were grouped together)3. In a first step we allocated costs directly to the inpatient ward when resource usage could be identified. This was for instance the case with personnel costs whereby medical staff were assigned a proportion of their time (and thus cost) to the inpatient ward based on interviews with the staff. Other costs that could not be assigned directly to the inpatient ward were allocated on the basis of criteria reflecting service use including floor space (for costs of maintenance, cleaning and utilities) and number of staff (for the administration costs).

Once all costs had been assigned to the inpatient ward, a unit cost per inpatient day was calculated by dividing the total cost of the inpatient ward with the total number of inpatient bed-days. Information about the number of inpatient bed-days at each facility was not readily available and was estimated by multiplying the number of admissions with the average length of stay (ALOS). The number of admissions of VL and non-VL patients was retrieved from the statistical records. The ALOS of VL patients was 30 days and obtained from the same sample of 250 medical records described above. The ALOS of non-VL patients was estimated by taking a random sample of 120 medical records at each facility and recording the date of admission and date of discharge4. The ALOS for non-VL patients ranged from 2 days at Kassab to 3.5 days at Doka hospital.

[2] World Health Organization, Choosing Interventions that are Cost Effective (WHO-CHOICE): http://www.who.int/choice/toolkit/cost_it/en/index.html

[3] None of the health facilities had disease-specific wards but were differentiated by gender and age (male, female and paediatric ward).

[4] At Kassab, all medical records of non-VL patients were consulted.

The median total cost of VL care from the provider perspective was obtained by multiplying the unit cost per inpatient day with the ALOS for a VL patient and adding to this figure the medical costs per VL patient obtained with the ingredients approach.

Costs from the household perspective

Costs from the household perspective included direct and indirect costs. These were collected with a hospital exit survey using a pre-tested structured questionnaire. A total of 75 patients were interviewed at Kassab hospital (n=45) and Bazora HC (n=30) between December 2010 and May 2011. At the time of the survey there were no patients attending Doka hospital due to a shortage of SSG at the hospital. The interviews were conducted in Arabic by a medical doctor with extensive experience in VL diagnosis and treatment (one of the authors, AA).

The monetary expenditures by patients and their family to access and receive VL services were recorded separately for all health care providers that were visited. Respondents were asked about all direct medical costs they incurred such as expenditure on registration fees, drugs, laboratory investigations and medical supplies at each provider. The survey also included questions on non-medical costs including the cost of transportation to and from the various health providers as well as food costs incurred while travelling to a health provider and during hospitalization at the treatment facility.

Indirect costs represented the loss of productive time of patients and family members taking care of the patient due to VL illness. Patients and their caretakers were asked about the number of days they were unable to engage in productive activities, and this was multiplied by a median daily income to obtain the indirect cost of a VL episode. Most patients and caretakers that contributed to the household income combined subsistence farming with casual labour during the off-season when there was no field work. To estimate the median daily income (as well as household income in general), the survey collected data on the economic activities of all household members, the number of months these activities were done and the daily or monthly income in the case of casual labour. For subsistence farming, information was collected on the annual production of each produce which was valued with local market prices and divided by the number of agriculturally active household members. Data was also gathered on the income from sales of animals and animal products (e.g. milk) and remittances from family members. Farming activities were done on average 6 months per year, while the rest of the year consisted of casual labour usually in construction (e.g. brick making) or the collection and sale of wood.

The direct and indirect costs were added together to obtain the median total cost of an episode of VL from the perspective of the household. The costs of VL were considered catastrophic if they exceeded 10% of the annual household income (O'Donnell *et al.* 2008; Ranson 2002).

Data analysis

The data was entered in Excel (Microsoft) and analysed with Excel and STATA v10.1 (Stata Corp., College Station Tx, USA). Cost data collected prior to 2010 were inflated using the consumer price index (World Bank 2012) to the year 2010. All cost data are presented in US$ whereby US$ 1 = SDP 2.64 (2010).

RESULTS

Costs from the provider perspective

Table 2 shows the median cost of VL case management per patient from the provider perspective as well as activity data for each of the three health facilities. The total cost includes both the "hotel" and the medical component.

Table 2: Activity statistics and unit costs by health facility

	Kassab hosp.	**Doka hosp.**	**Bazora hosp.**
Area covered	Between Rahad and Atbara rivers	Between Rahad and Atbara rivers	Rahad river basin
Beds	68	82	51
Admissions VL (non-VL)	805 (95)	102 (3,049)	580 (1,198)
In-patient days VL (non-VL)	24,150 (187)	3,060 (10,641)	17,400 (3,810)
Total in-patient days	*24,337*	*13,701*	*21,210*
Average length-of-stay VL (non-VL)[1]	30 (2)	30 (3.5)	30 (3)
Bed occupancy rate	111%	46%	114%
Median cost per patient (IQR) (US$)	154 (137-186)	366 (349-399)	117 (100-147)

[1] The ALOS was estimated from a random sample of medical records of VL and non-VL patients.

There were marked differences in the median total cost per patient between facilities ranging from US$117 at Bazora, US$155 at Kassab and US$366 at Doka hospital. The medical cost of VL represented 13%, 30% and 38% of total costs at Doka, Kassab and Bazora respectively. The median medical cost was US$45 (IQR $28-$75) per patient with the cost of SSG representing 91% of medical costs. The large variation between facilities in the total cost per patient was caused by the difference in the (hotel) unit cost per inpatient day. While the unit cost per inpatient day was similar at Bazora and Kassab hospitals (US$2.5 and US$3.8 respectively), it was nearly 3 times higher at Doka hospital compared to Kassab (US$11 per inpatient day).

Varying the discount rate between 0% and 10% did not have much impact on the cost per inpatient day. At Bazora hospital, where capital costs as a proportion of total hospital costs were the largest (23% vs. 12% at Kassab and 11% at Doka), the unit cost per inpatient day changed from US$ 2.1 (0% discount rate) to US$ 2.5 (10% discount rate).

Costs from the household perspective

Patient and household characteristics

A total of 75 patients attending Kassab (n=45) and Bazora hospital (n=30) were interviewed; we did not interview any patients at Doka hospital because of a shortage of VL drugs at the time of the study. The cost data from the household perspective collected from Kassab and Bazora hospital were combined in the analysis (tables 3 and 4). Site-specific household cost data is provided in appendix 1.

The majority of patients were males (68.0%) and young with 60% of patients below the age of 15 corresponding to the age profile of other studies showing the epidemic in East Africa is concentrated amount the young. The median age of the sample was 13 (range 3 to 40); female patients were younger than males (median 7.5 (range 2-34) vs. 13 (range 2-40); $p<0.05$). Overall the level of education was low. Amongst patients aged 6 and above (n=61), 29 (47.5%) had not received any formal education (including Koranic schools). Only 3 patients had completed primary school. There were major differences in the level of education between males and females whereby male patients were more likely to have received some primary education ($p<0.01$). The median household size was 6 members.

Twenty-nine per cent of patients were economically active (n=22), mainly engaged in subsistence farming (n=13; 59.1%) and daily labour (n=7; 31.9%). Two patients were formally employed. Of those engaged in farming, 7 patients were working as casual labourers during the off-season (defined as secondary occupation). The median annual income of working patients was US$ 471 (IQR US$ 244-1,049).

Subsistence farming was the principal economic activity for 80% of households (n=60). A median of two different crops were cultivated by the same household (IQR 2-3; range 1-4); sorghum was the most common crop, followed by sesame, millet and peanuts. Although 40% of households reported owning livestock, either sheep, goats and/or cattle, the headcount was

low and only 47% of these households sold livestock over the past year (n=14) contributing to 6% of their household income. About 19% of households reported receiving remittances, nearly all from outside Sudan (92.9%). The median amount of remittances received was US$ 378 per year (IQR US$ 114-454). Including all sources of income, the median annual household income was US$1,116 (IQR US$ 744-1,818) and the median annual per capita income was US$ 208 (IQR US$ 140-341).

Direct costs at health providers prior to admission

Prior to admission for treatment at Kassab or Bazora hospital, patients had visited on average 3 other health providers (IQR 2-4). A public provider - either a village health worker (43%), a health centre (20%) or a hospital (25%) - was most often the first choice of provider mainly due to their proximity to the patients' home while the remainder of patients visited either a chemist (3%) or a private general practitioner (9%). Because there are few private (formal) health providers in rural areas, less than 10% of households had initially visited a private provider. In subsequent visits, households consulted a private general practitioner more frequently (24% of households had consulted a private general practitioner after the first provider) or a public hospital until eventually all patients consulted or were referred to either Kassab or Bazora hospital and admitted for treatment.

Households incurred a median total cost of US$ 33 during the health seeking phase (IQR US$ 9-73) (table 3) and this included expenses on consultation (US$ 1), drugs (US$ 14), laboratory investigations (US$ 3) and transportation (US$ 1) (table 4). Households paid the most at private formal providers (US$ 51), twice as much as at public hospitals (US$ 24) ($p<0.01$), of which 94% were direct medical costs for consultation, drugs and diagnosis/laboratory investigations. Households that visited private laboratories were usually referred by a previous provider to be tested for VL.

Direct costs at the treatment facility

The combined direct medical and non-medical costs by households for Kassab and Bazora hospital are presented in table 4. All interviewed patients were treated with sodium stibogluconate; our study confirmed that sodium stibogluconate was provided free of charge to patients in these two facilities. Very few laboratory investigations were done once the patient was admitted. The median direct medical cost was US$ 14 (IQR US$ 10-22). Over 85% of costs were non-medical, mainly food costs (median US$ 112) caused by the long stay at the hospital (median 30 days). The food costs were for the patient, caretaker(s) and other accompanying relatives. All patients were accompanied by at least one adult caretaker, usually the mother,

Table 3: Mean/median cost per provider visited during the health seeking phase prior to admission (US$ 2010)

Health provider	n	Mean	(sd)	Median	(IQR)
Traditional healer	3	10.2	(9.2)	10.2	(3.7-16.7)
Chemist	2	8.7	(4.5)	8.7	(5.6-11.9)
VHW	37	14.6	(19.8)	9.3	(4.5-16.0)
Public health centre	22	33.3	(44.7)	15.3	(10.0-42.8)
Public hospital	30	56.8	(73.8)	24.2	(12.1-55.8)
Private doctor	26	90.7	(125.4)	51.2	(32.7-101.2)
Private laboratory	13	27.9	(16.8)	26.0	(17.9-34.2)
Total cost per person	75	60.8	(103.5)	33.1	(9.3-73.3)

Note: All data presented in this table was calculated using data collected at 2 hospitals (Kassab and Bazora). Household costs by facility are provided in appendix table A.1

and one or two young children that stayed with the patient at the hospital for the full duration of treatment. The median direct cost of VL care at the treatment facility was US$ 148 (IQR US$ 128-184).

Indirect costs of VL

Sixteen out of 22 patients (73%) reported they were unable to carry out either their primary or secondary occupation because of VL illness which resulted in an income loss. The median number of workdays lost was 51 days (IQR 44-63). The median loss of income for working patients was US$ 101 (IQR US$ 62-233) while the average loss of income across all patients was US$ 41 (sd US$ 135). Among adult caretakers, 20 reported an income loss (out of 99 caretakers), with a median loss of 39 working days (IQR 31-58) because they had to take care of the patient. The median loss of income to caretakers was US$ 95 (IQR US$ 45-179). The average income loss across all attendants, both working and non-working was US$ 44 (sd US$ 85).

Total costs of a VL episode

The median total cost for one VL episode was US$ 450 (IQR US$ 387-544) (table 5). The median cost of VL case management across the three health facilities was US$ 211 (IQR US$ 197-244). The median direct expenditure by households, including the health seeking phase and the costs incurred at the treatment facility, was US$ 185 (IQR US$ 158-240) while the median income loss (i.e. indirect costs) was US$ 22 (IQR US$ 0-113.9). Overall, households bore 53% of the total cost of VL and public health facilities 47%. Direct costs, in particular non-medical costs, were the main cost driver from the perspective of the household representing nearly 86% of the

Table 4: Mean/median direct costs of VL care during the health seeking and treatment phase (US$ 2010)

	Health seeking phase				Admission & treatment			
	Mean	**(sd)**	**Median**	**(IQR)**	**Mean**	**(sd)**	**Median**	**(IQR)**
Direct medical costs								
Consultation	6.6	(13.0)	1.1	(0.0-6.0)	3.3	(1.7)	3.7	(1.1-4.8)
Ancillary drugs	26.0	(47.7)	13.8	(6.7-37.2)	11.1	(10.0)	7.4	(4.3-15.6)
Laboratory investigations	13.2	(24.9)	3.3	(0.0-16.7)	4.1	(7.0)	1.9	(0.2-4.1)
Total direct medical costs	45.9	(78.4)	24.2	(9.3-54.0)	18.5	(14.9)	14.0	(9.9-22.3)
Direct non-medical costs								
Transportation	7.5	(14.7)	1.1	(0.0-7.4)	6.5	(10.1)	2.6	(0.7-8.9)
Food	6.5	(19.9)	0.0	(0.0-4.8)	121.5	(44.5)	111.6	(111.6-141.4)
Other	1.0	(4.4)	0.0	(0.0-0.2)	5.0	(4.1)	4.5	(2.0-6.9)
Total direct non-medical costs	15.0	(31.1)	2.6	(0.0-18.6)	133	(46.0)	126.5	(113.9-157.8)
Total direct costs	60.8	(103.5)	33.1	(9.3-73.3)	151.5	(49.1)	148.5	(128.2-184.2)

Note: All data presented in this table was calculated using data collected at 2 hospitals (Kassab and Bazora). Household costs by facility are provided in appendix tables A.2 and A.3

median household cost while indirect costs represented 14% of this cost. The median annual household income was estimated to be US$ 1,116. The economic burden of VL to households, including direct and indirect costs, was equal to 23% of the median annual household income.

Table 5: Summary of direct and indirect costs for one VL episode (US$ 2010)

	Mean	**(sd)**	**Median**	**(IQR)**
Direct costs				
Household[1]	212.4	(122.8)	185.1	(158.5-240.2)
Provider[2]	220.3	(31.4)	211.1	(197.3-243.9)
Indirect costs	118.8	(181.9)	22.3	(0-113.9)
Total cost				
Household	297.1	(250.4)	238.4	(171.8-333.2)
Household + provider	508.2	(250.3)	450.0	(386.9-544.3)
Median costs as a % of				
Annual household income	23%			
Annual per capita income	122%			

[1] Health seeking and treatment facility costs; Calculated using the mean/median data from 2 hospitals (Kassab and Bazora) since no patients attended Doka hospital at the time of the study

[2] Calculated using the average hotel unit cost of US$ 5.74 across the three hospitals

DISCUSSION

This is the first study to provide a comprehensive set of estimates on the cost and economic burden of VL in Sudan and East Africa in general. We collected data from both the provider and the household perspective. Data on provider costs were collected from three health facilities in Gedaref State; direct costs to access treatment and indirect costs of VL illness from the perspective of the household were collected using a structured exit questionnaire with 75 patients in two of these facilities.

The median total cost per episode of VL was estimated to be US$ 450. Over 75% of households incurred catastrophic out-of-pocket expenditures (defined as expenditures exceeding 10% of annual median income) when considering only direct costs while 83% of households exceeded this threshold when also including indirect costs. These findings concur with studies that were carried out in the Indian subcontinent (Nepal, India and Bangladesh) which also found a huge economic burden of VL illness for households (Meheus *et al.* 2006; Rijal *et al.* 2006; Sarnoff *et al.* 2010; Sundar *et al.* 2010; Uranw *et al.* 2013). There were however some differences with regard to the distribution of costs. Indirect cost as a proportion of the total household cost

was smaller in Sudan, mainly linked with a different age profile. In our study we found that 60% of patients were below the age of 15 while for instance in Bangladesh it was 47% [3.] These differences are consistent with the demographic profile of VL across countries reported by Harhay *et al.* (2011). Because patients were younger in Sudan, fewer reported earning an income. For instance we found that 29% of patients were economically active and generating an income to the household compared to 36% in Nepal (Uranw *et al.* 2013) and 42% in India (Meheus *et al.* 2006).

In terms of the provider costs, the cost of hospitalization (which did not include the medical costs of VL) was the main cost driver and varied between 62% and 87% of the total provider cost at Bazora and Doka hospital respectively. We observed large differences in the unit cost per inpatient day across the three facilities. There are several factors that explain the higher unit cost per inpatient day at Doka hospital. From the cost side, because Doka hospital is a secondary level referral facility, it has more skilled health staff resulting in higher personnel costs. For instance the ratio of medical doctors working at Doka compared to Bazora hospital was 5:1. The capital costs were also higher compared to the other two health facilities. But the factor that influenced the unit cost most was the workload at each hospital, and in particular the number of VL patients. Because most costs are fixed (including personnel costs on the short and medium term) and do not vary with the number of inpatients at the hospital, the fewer the inpatients, the higher the unit cost per inpatient day. A total of 1,487 patients were admitted for VL treatment in the three study facilities in 2008, with important differences in case load across facilities. Overall the bed occupancy5 rate at Doka hospital was low (46%) while in Kassab and Bazora it exceeded 100% (on average, there were not sufficient beds to accommodate all patients). Doka hospital admitted the least VL patients in 2008 due to frequent shortages of SSG. These patients were then referred to Kassab hospital, located approximately 50kms away. The number of VL patients at Bazora hospital was high because the hospital covers a very large area (the Rahad River Basin) with important transmission of VL.

Our estimates were also lower than the WHO-CHOICE hotel unit cost estimates for Sudan (i.e. US$ 13.5 inflation-adjusted for a secondary-level hospital at 80% occupancy rate) (WHO-CHOICE 2012). The variation in unit costs between facilities in this study was caused by differences in the cost structure of the health facilities, but especially by the patient load since we observed a low occupancy rate at Doka hospital (46%) and rates exceeding full occupancy at Kassab and Bazora. During the time of the study, most VL patients who attended Doka hospital were referred to Kassab hospital because of a shortage in SSG drugs. Given these

[5] The bed occupancy rate was calculated as the number of inpatient days in a year divided by the number of beds x 365.

logistical problems the unit costs of hospitalization should be interpreted with care and not considered as an indicator of efficient resource usage. As Hansen *et al.* (200) noted in a study on the hospital costs of HIV/AIDS care, low unit costs may also indicate insufficient resources at these health facilities. Although an evaluation of optimal resource usage for VL care and other services was not within the scope of this study, there were clear indications that for example the hospital in Bazora was under-staffed compared to its patient load.

A limitation to our study was that we did not capture the seasonal pattern of costs. While this is less relevant for provider costs that were based on data for a complete financial year, the household survey was carried out half-way the dry season, which takes place approximately from November to April. This may have had an impact on the health seeking behaviour of households and transportation costs. Since health facilities are more accessible during the dry season, patients are likely to present faster to a health facility and transportation costs will be lower. For example, Gerstl *et al.* (2006) in a study examining the accessibility of VL treatment centres in Gedaref State found that transportation costs were 2 to 3 times higher during the rainy season. In addition the time of the survey may also have had an impact on the opportunity cost of time lost due to VL illness and treatment. Patients involved in subsistence farming reported they were not working at the time of the survey because it was the off-season. As such we may have underestimated the indirect cost of VL illness for those patients that did not have a secondary occupation.

Secondly, data on costs were based on actual consumption of resources with the major cost elements (medical costs and personnel) obtained through micro-costing. However the hospital records on activity statistics were poor and the unit costs per inpatient day are particularly sensitive to inaccurate activity data. Information on the number of admissions for both VL and non-VL patients were available at each facility, but the average length of stay needed to be extrapolated from a random sample of medical records. While the average length of stay for VL patients is no doubt close to 30 days because of the duration of the drug regimen, there was more uncertainty regarding the ALOS of non-VL patients.

Finally, we were not able to obtain data for all cost categories at each hospital included in the study. From the provider perspective, detailed information from medical records to estimate the direct medical costs was only available at Kassab hospital. Data from the household perspective was collected from Kassab and Bazora hospital and not Doka hospital since there were no patients attending the latter facility at the time of the study due to a shortage of SSG. Given the limitations in data availability and since the aim of the study was to estimate the cost of

providing and accessing VL diagnosis and treatment services, rather than making comparisons across facilities (in terms of e.g. efficiency or access), results were presented in terms of the mean/median across the three facilities. This is the first study of its kind for VL carried out in Sudan (and eastern Africa in general). We hope that in the future, cost data on VL diagnosis and treatment will be more readily available to support on-going control efforts in the country.

In the absence of a vaccine and preventive interventions, the diagnosis and treatment of VL is currently the main control strategy available in Sudan. We showed VL diagnosis and treatment to be expensive not only to the public health sector but also to the households compared to their income. Policies are therefore needed that reduce this cost to both providers and households. A common determinant of costs for both perspectives was the length of treatment. The current first line treatment is SSG and patients are admitted for the full duration of treatment of 30 days to ensure adherence to treatment and monitor for possible side-effects. In recent years there have been a number of therapeutic innovations that open the door to treatment alternatives with shorter duration. These treatment alternatives would not only reduce the cost of hospitalization from the provider perspective but also the substantial food costs patients and caretakers incur. One of the alternatives is a combination of SSG and paromomycin for 17 days (Melaku *et al.* 2007) that showed an acceptable safety and efficacy profile in a recent randomized-controlled trial (Musa *et al.* 2012). This treatment is in fact now being rolled out in Gedaref state. Other alternatives include combinations of an oral drug miltefosine with either SSG or liposomal amphotericin B (Omollo *et al.* 2011) that may reduce treatment to 10 days (for the latter combination) or a multi-dose regimen of liposomal Amphotericin B for 10 days (Edwards *et al.* 2011). Liposomal Amphotericin B (AmBisome®) is already registered in Sudan and used as second line treatment but is not considered as first-line because of its very high cost despite preferential pricing agreements between the WHO and its manufacturer Gilead Sciences (US$ 270 for total dose of 21 mg/kg for a 35kg patient). However a donation by Gilead to treat 50,000 patients opens new perspectives for using AmBisome® as first line treatment in East Africa (Burki 2012).

The cost data that we presented here will facilitate the use of cost-effectiveness analysis to compare the various treatment alternatives presently available or in the near future for Sudan. This study highlighted the importance of including the household perspective in such analysis since VL caused catastrophic health expenditure in almost all households despite drugs and diagnostics being free. In the absence of effective prevention, the best way to alleviate this burden is through a treatment regimen with shorter duration. The article is hopefully the first in a series of studies investigating the behavioural and socio-economic aspects of VL and its control. Until we are able to close this knowledge gap, there will be little interest from the

government and the international community to actively engage in the control of VL in Sudan and East Africa in general.

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Table A. I: Mean/median cost per provider visited during the health-seeking phase prior to admission (US$ 2010)

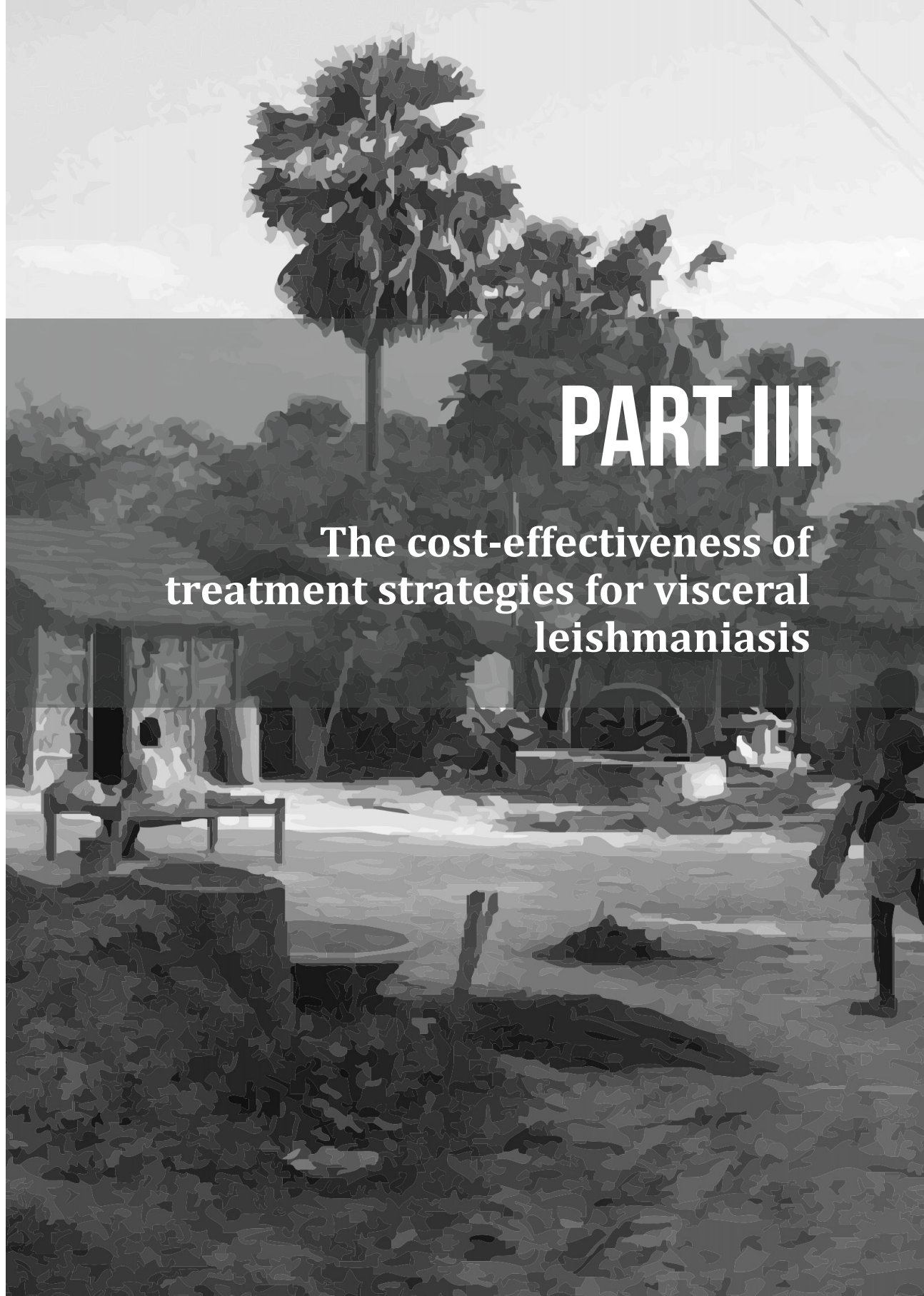
	Bazora						Kassab						Total					
	n	mean	sd	median	p25	p75	n	mean	sd	median	p25	p75	n	mean	sd	median	p25	p75
Traditional healer	0						3	10.2	9.2	10.2	3.7	16.7	3	10.2	9.2	10.2	3.7	16.7
Chemist	1	5.6		5.6	5.6	5.6	1	11.9		11.9	11.9	11.9	2	8.7	4.5	8.7	5.6	11.9
VHW	16	20.2	28.9	11.2	7.8	20.8	21	10.4	6.7	9.1	4.3	14.0	37	14.6	19.8	9.3	4.5	16.0
Public health centre	6	54.2	73.2	27.3	12.3	47.3	16	24.4	23.9	12.8	9.3	38.3	22	33.3	44.7	15.3	10.0	42.8
Public hospital	8	36.0	50.5	13.9	10.1	40.9	22	65.5	81.3	29.0	13.8	99.5	30	56.8	73.8	24.2	12.1	55.8
Private doctor	4	73.7	59.3	93.0	7.1	120.9	22	94.6	137.7	47.3	35.7	89.7	26	90.7	125.4	51.2	32.7	101.2
Private laboratory	0						13	27.9	16.8	26.0	17.9	34.2	13	27.9	16.8	26.0	17.9	34.2
Total cost per person	30	38.1	54.7	15.9	4.5	40.9	45	76.0	124.3	43.2	21.2	80.7	75	60.8	103.5	33.1	9.3	73.3

Table A.2: Mean/median direct costs of VL care during the health seeking phase (US$ 2010)

	Bazora					Kassab					Total				
	mean	**sd**	**median**	**p25**	**p75**	**mean**	**sd**	**median**	**p25**	**p75**	**mean**	**sd**	**median**	**p25**	**p75**
Direct medical costs															
Consultation	4.2	11.3	0.0	0.0	2.2	8.2	13.9	2.2	0.0	7.4	6.6	13.0	1.1	0.0	6.0
Ancillary drugs	16.9	17.5	11.2	3.7	26.0	32.1	59.4	18.2	8.2	38.0	26.0	47.7	13.8	6.7	37.2
Laboratory investigations	5.2	9.2	0.6	0.0	8.6	18.6	30.2	7.4	1.1	24.2	13.2	24.9	3.3	0.0	16.7
Total direct medical costs	*26.3*	*31.2*	*13.4*	*4.5*	*40.9*	*58.9*	*96.2*	*35.7*	*21.2*	*65.7*	*45.9*	*78.4*	*24.2*	*9.3*	*54.0*
Direct non-medical costs															
Transportation	7.6	19.3	0.0	0.0	4.5	7.3	10.9	2.2	0.0	10.4	7.5	14.7	1.1	0.0	7.4
Food	3.1	7.6	0.0	0.0	0.0	8.7	24.8	0.9	0.0	5.2	6.5	19.9	0.0	0.0	4.8
Other	1.1	5.2	0.0	0.0	0.2	1.0	3.8	0.0	0.0	0.2	1.0	4.4	0.0	0.0	0.2
Total direct non-medical costs	*11.9*	*26.9*	*0.0*	*0.0*	*5.6*	*17.1*	*33.7*	*4.7*	*0.0*	*21.6*	*15.0*	*31.1*	*2.6*	*0.0*	*18.6*
Total direct costs	38.1	54.7	15.9	4.5	40.9	76.0	124.3	43.2	21.2	80.7	60.8	103.5	33.1	9.3	73.3

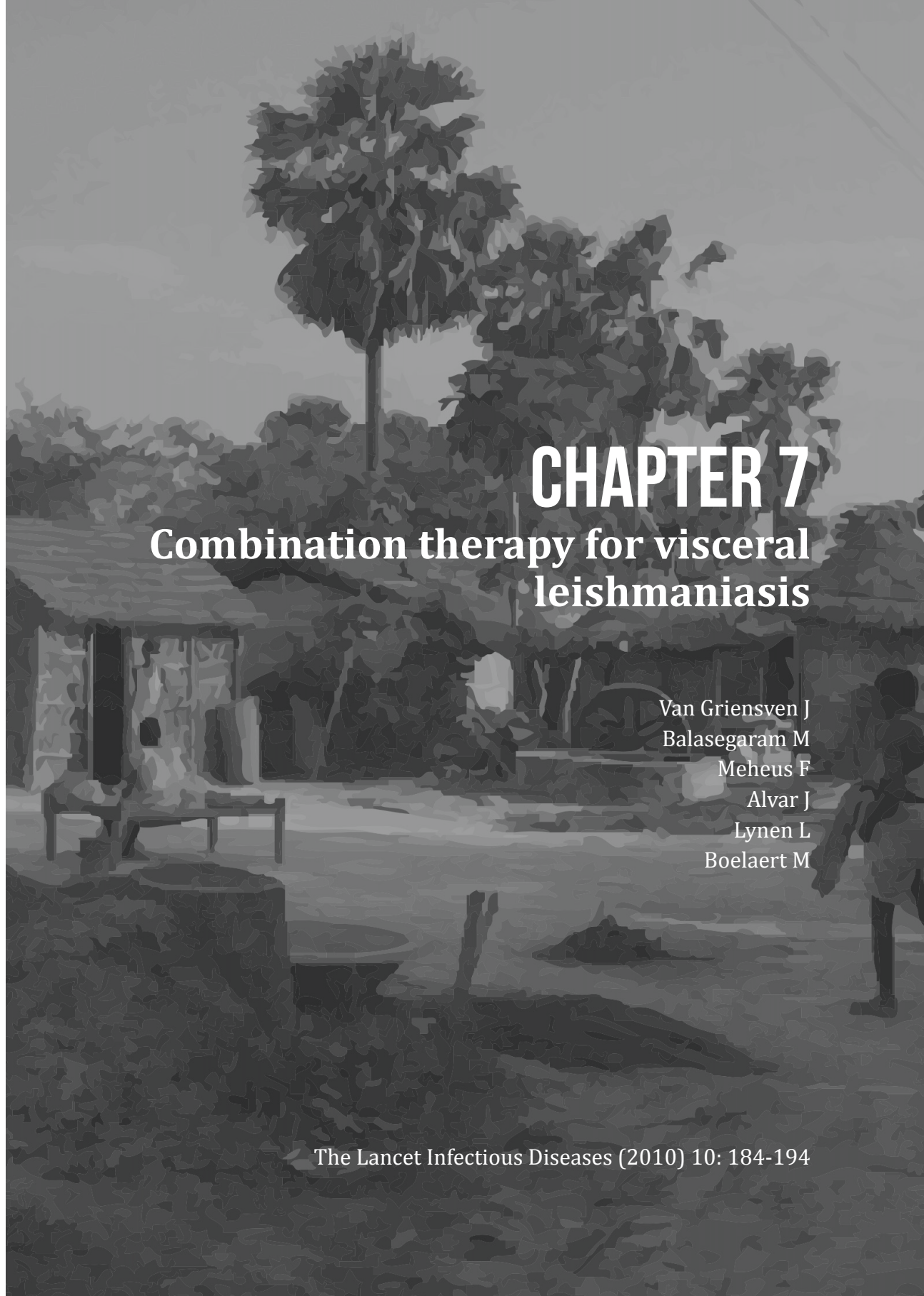
Table A.3: Mean/median direct costs of VL care at the treatment facility (US$ 2010)

	Bazora					Kassab					Total				
	mean	**sd**	**median**	**p25**	**p75**	**mean**	**sd**	**median**	**p25**	**p75**	**mean**	**sd**	**median**	**p25**	**p75**
Direct medical costs															
Consultation	1.7	1.3	1.1	1.1	2.2	4.5	0.9	4.8	4.8	4.8	3.3	1.7	3.7	1.1	4.8
Ancillary drugs	18.0	11.5	16.4	11.2	22.3	6.5	5.1	5.6	2.6	7.4	11.1	10.0	7.4	4.3	15.6
Laboratory investigations	8.3	9.6	4.8	3.3	9.7	1.3	1.5	0.7	0.0	1.7	4.1	7.0	1.9	0.2	4.1
Total direct medical costs	*28.0*	*18.9*	*23.3*	*18.6*	*29.0*	*12.3*	*6.0*	*11.5*	*7.8*	*14.0*	*18.5*	*14.9*	*14.0*	*9.9*	*22.3*
Direct non-medical costs															
Transportation	7.4	11.3	3.7	0.7	7.4	5.9	9.3	1.9	0.7	8.9	6.5	10.1	2.6	0.7	8.9
Food	116.0	50.3	111.6	111.6	141.4	125.2	40.3	111.6	111.6	137.7	121.5	44.5	111.6	111.6	141.4
Other	5.3	4.2	4.9	3.5	6.1	4.8	4.1	3.7	1.9	6.9	5.0	4.1	4.5	2.0	6.9
Total direct non-medical costs	*128.7*	*50.5*	*121.1*	*112.4*	*155.5*	*135.8*	*43.0*	*128.0*	*114.4*	*158.9*	*133.0*	*46.0*	*126.5*	*113.9*	*157.8*
Total direct costs	156.6	56.6	149.4	136.2	184.2	148.1	43.8	148.5	124.8	172.5	151.5	49.1	148.5	128.2	184.2



PART III

The cost-effectiveness of treatment strategies for visceral leishmaniasis



CHAPTER 7

Combination therapy for visceral leishmaniasis

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SUMMARY

Combination therapy for the treatment of visceral leishmaniasis has increasingly been advocated as a way to increase treatment efficacy and tolerance, reduce treatment duration and cost, and limit the emergence of drug resistance. We reviewed the evidence and potential for combination therapy, and the criteria for the choice of drugs in such regimens. The first phase 2 results of combination regimens are promising, and have identified effective and safe regimens as short as 8 days. Several phase 3 trials are underway or planned in the Indian subcontinent and east Africa. The limited data available suggest that combination therapy is more cost-effective and reduces indirect costs for patients. Additional advantages are reduced treatment duration (8—17 days), with potentially better patient compliance and lesser burden on the health system. Only limited data are available on how best to prevent acquired resistance. Patients who are co-infected with visceral leishmaniasis and HIV could be a reservoir for development and spread of drug-resistant strains, calling for special precautions. The identification of a short, cheap, well-tolerated combination regimen that can be given in ambulatory care and needs minimal clinical monitoring will most likely have important public health implications. Effective monitoring systems and close regulations and policy will be needed to ensure effective implementation. Whether combination therapy could indeed help delay resistance, and how this is best achieved, will only be known in the long term.

INTRODUCTION

Visceral leishmaniasis, also known as kala-azar, is a disseminated protozoan infection caused by the *Leishmania donovani* complex and transmitted via phlebotomine sandflies (Chappuis *et al.* 2007). The zoonotic form, for which dogs are the main reservoir, is present in the Mediterranean basin, China, the Middle East, and South America, and is caused by *Leishmania infantum* or *Leishmania chagasi*. The anthroponotic form (human reservoir) is caused by *L donovani* and is prevalent in east Africa and the Indian subcontinent (Chappuis *et al.* 2007; Herwaldt 1999). Although the disease is endemic in more than 60 countries, with 200 million people at risk, 90% of the 500 000 cases every year happen in five countries: India, Bangladesh, Nepal, Sudan, and Brazil (figure 1) (Chappuis *et al.* 2007; Desjeux 2004a; Guerin *et al.* 2002; Desjeux 2004b).

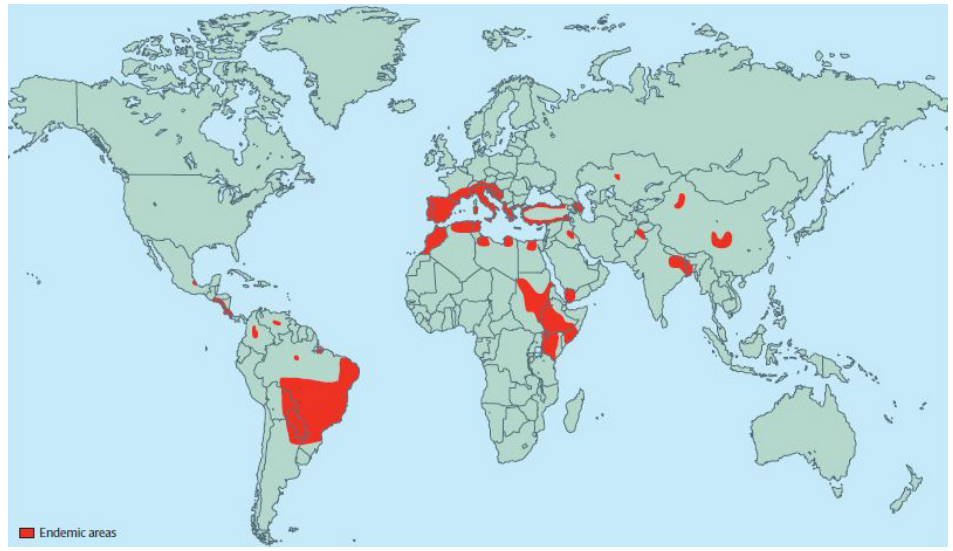

Figure 1: Geographical distribution of visceral leishmaniasis

Anthroponotic visceral leishmaniasis happens mainly in east Africa and the Indian subcontinent. The zoonotic form is prevalent in South America, the Mediterranean basin, China, and the Middle East. More than 90% of cases happen in five countries: India, Nepal, Bangladesh, Sudan, and Brazil. Reprinted from Desjeux (2004b) with permission from Macmillan Publishers Ltd.

For most of the past 70 years, the therapeutic armoury for treatment of visceral leishmaniasis has been extremely limited (Alvar *et al.* 2006). Pentavalent antimonials were introduced in the 1940s, and include sodium stibogluconate and meglumine antimoniate. Use of amphotericin

B followed after a few decades, and was later joined by paromomycin, a cheap and effective parenteral drug with an acceptable toxicity profile that can easily be given by intramuscular injection (Sundar *et al.* 2008). The development of miltefosine, the only drug at present that can be given orally for visceral-leishmaniasis treatment, has been a major breakthrough (Berman 2006; Croft *et al.* 2006). This drug is the mainstay of the recently launched visceral-leishmaniasis elimination plan in the Indian subcontinent, (WHO 2004) and benefits from a preferential pricing scheme that puts it at the same price as generic pentavalent antimonials if large quantities are purchased. Finally, different lipid formulations of amphotericin B (ie, liposomal amphotericin B) have been developed, which are similar to amphotericin B in efficacy but with fewer toxic effects (table 1) (Bern *et al.* 2006). Although these formulations were initially prohibitively expensive, the preferential price now offered to governments of endemic countries, WHO, and non-governmental organisations make them an option for low-income and middle-income countries. Although other compounds are being developed, these drugs are likely to constitute the main therapeutic options for visceral leishmaniasis in the years to come (Alvar *et al.* 2006; Maltezou 2008). These drugs belong to chemically unrelated classes and are thought to have distinct targets. All of them have several important disadvantages (table 1).

There are several reasons why consensus has grown over the past few years towards the use of combination regimens in visceral leishmaniasis (Alvar *et al.* 2006; Bryceson 2001; Croft *et al.* 2006; Den Boer *et al.* 2006; Sundar *et al.* 2007; Singh *et al.* 2006). First, combining drugs from different chemical classes could reduce treatment duration or total drug doses, resulting in fewer toxic effects, higher compliance, and less burden on the health system. This could also reduce the overall costs (direct and indirect) and provide a more cost-effective option. Increasing reports of treatment failure with pentavalent antimonials from the Indian subcontinent have raised the issue of acquired drug resistance (Croft *et al.* 2006; Lira *et al.* 1999; Sundar 2001). This concern now extends to miltefosine, because of its long half-life and susceptibility to develop resistance with a single point mutation (Sundar *et al.* 2005; Perez-Victoria *et al.* 2006; Seifert *et al.* 2007. Combination therapy might help to delay the emergence of resistance and increase the therapeutic lifespan of the respective drugs, as has been seen for diseases like malaria, tuberculosis, and HIV (Bryceson 2001). Finally, combination therapy could improve treatment efficacy for complicated cases, such as patients coinfected with HIV, for whom treatment outcomes with monotherapy have been consistently poor (Alvar *et al.* 2008). We review the evidence and explore the potential of combination therapy for visceral leishmaniasis in areas of anthroponotic transmission—in particular, the Indian subcontinent and east Africa. Given the anthroponotic pattern, these areas have the highest threat of drug resistance and bear the highest burden of visceral leishmaniasis. We will discuss the evidence and the criteria for a rational design of such combination regimens that focus on the parallel or

Table 1: Drugs currently used for treatment of visceral leishmaniasis

	Marketing* (trade name of drug)	Regimen	Clinical efficacy	Resistance	Toxicity	Cost of drug course (US$)	Disadvantages
Pentavalent Antimonials (sodium stibogluconate, meglumine antimoniate)	Sodium stibogluconate: Albert David (SSG), GlaxoSmihKline (Pentostam). Meglumine antimoniate: Sanofi Aventis (Glucantime)	20 mg antimony per kg bodyweight for 20-30 days (depending on geographic area), intravenous or intramuscular	35-95% (depending on geographic area)	Treatment failure up to 60% (Bihar, India)	Moderately toxic: cardiac effects, pancreatitis, nephrotoxicity hepatotoxicity	53 (generic) to 198 (branded SSG)	Quality control; length of treatment; painful injection; resistance in India
Amphotericin B	Bristol Meyers Squibb (Fungizone); generic companies	1 mg/kg every other day for up to 30 days (15 mg/kg total dose), intravenous	> 97% all regions	Not documented	Moderately toxic: nephrotoxicity (inpatient care needed)	About 21 (generic)	Need for slow intravenous infusion; dose-limiting nephrotoxicity; heat stability
Liposomal amphotericin B	Gilead (AmBisome)	5-20 mg/kg total dose in 4-10 doses over 10-20 days, intravenous	Asia: > 97%; India, single dose: 91%; Africa: not fully established	Not documented	Nephrotoxicity (limited)	280 (preferential) for 20mg/kg dose; about 3000 (non-preferential)	Price; need for slow intravenous infusion; heat stability (needs to be stored below 25°C)
Miltefosine	Paladin, Montreal, Canada (Impavido)	2-2.5 mg/kg daily over 28 days (India only), oral	Asia: 94% (India); Africa: 60% (single field study), 93% in patients not infected with HIV and excluding those lost to follow up	Only in laboratory isolates	Gastrointestinal effects (20-55% of patients, usually mild), nephrotoxicity hepatotoxicity possibly teratogenic	About 74 (preferential), about 150 (non-preferential)	Price; possibly teratogenic; potential for resistance (half-life); poor patient compliance
Paromomycin sulphate	Institute for One World Health; †Gland Pharma, Hyderabad, India	15 mg/kg daily for 21 days (India only), intramuscular	Asia: 94% (India); Africa: under evaluation	Only in laboratory isolates	Nephrotoxicity ototoxicity hepatotoxicity (all relatively rare)	About 15	Efficacy varies between and within regions; potential for resistance?

* Marketing authorization holder. † Paromomycin was granted orphan drug status by the US Food and Drug Administration and the European Medicines Agency in 2005. Adapted with permission from the Drugs for Neglected Diseases initiative from data presented during Fourth World Congress on Leishmaniasis (Feb 3-7, 2009).

sequential administration of separate drugs (co-administration), and are not co-formulations as used for tuberculosis or malaria.

EFFICACY AND SAFETY

Preclinical data

Few preclinical data on the efficacy and safety of combination therapies for visceral leishmaniasis are available. An early study looked at interactions between sodium stibogluconate and paromomycin (Neal *et al.* 1995). Whereas a marked potentiation was reported against *L donovani* in vitro, a less-pronounced, additive effect of the antimonial drug was noted in mice (Neal *et al.* 1995). Another study specifically focused on interactions in efficacy between miltefosine and sodium stibogluconate, amphotericin B, paromomycin, and sitamaquine (an oral aminoquinoline) (Seifert *et al.* 2006). In vivo, the highest enhancement of miltefosine activity was seen with amphotericin B, which preceded paromomycin. No activity enhancement was seen with miltefosine combined with sodium stibogluconate. Whereas the combination of miltefosine and amphotericin B could theoretically have some advantages over the other combinations, its clinical relevance remains unknown. More recent findings have also shown a synergistic interaction between amphotericin B and paromomycin (Seifert *et al.* 2009).https://vpnua2.ua.ac.be/+CSCO+dh756767633A2F2F6A6A6A2E677572796E617072672E70627A++/journals/laninf/article/PIIS1473-3099(10)70011-6/fulltext - bib26 Preclinical studies on several drug combinations have been done, with no major safety concerns identified (R Don, Drugs for Neglected Diseases initiative, personal communication, Jan 15, 2010).

Clinical data

The combination of pentavalent antimonials and paromomycin was the first regimen to be studied in India, at a time when clinical failure with pentavalent antimonials was increasingly being reported (Oliaro *et al.* 2005). Overall, these studies showed that 21-day regimen of paromomycin as monotherapy or combined with pentavalent antimonials were efficacious for visceral leishmaniasis. Subsequently, promising data became available on (shortened) monotherapy regimens. A phase 2 study showed that even with liposomal amphotericin B given as a single dose (5 mg/kg), a high proportion of patients could be cured (about 90%) (Sundar *et al.* 2011b; Sundar *et al.* 2003). Equally high proportions could be achieved with 14 days of miltefosine (Sundar *et al.* 2000). These observations provided the rationale for a phase 2, non-comparative randomised trial in India, which assessed different combinations of a single dose of liposomal amphotericin B followed by miltefosine for 7—14 days (table 2) (Sundar *et al.* 2008b). All combinations were highly efficacious (more than 95% of patients cured) and well tolerated, irrespective of the duration of miltefosine treatment. A phase 2 trial studying the combination of liposomal amphotericin B (5 mg/kg) with miltefosine for 14 days is underway in India and planned in Bangladesh (B Arana, WHO Special Programme for Research and Training in Tropical Diseases, personal communication, Nov 3, 2009) (ClinicalTrials.gov.a). Several short combinations are being studied in a large non-inferiority phase 3 trial in India (table 2), (ClinicalTrials.gov.b) which has now moved into its second stage adding children into the study. In 2009, similar studies will be started in Bangladesh and Nepal; the first results from India are expected by 2010.

In Africa, combination therapy of sodium stibogluconate and paromomycin was studied in the late 1980s, (Chunge *et al.* 1990) and was subsequently used by Médecins Sans Frontières, who needed a shorter treatment regimen when faced with large numbers of patients during an epidemic in Sudan (Davidson *et al.* 2009; Melaku *et al.* 2007; Seaman *et al.* 1996; Seaman *et al.* 1993). Retrospective cohort data from more than 4000 patients showed that, relative to monotherapy with pentavalent antimonials (sodium stibogluconate), combination therapy was associated with clearly reduced mortality and fewer complications during treatment (Melaku *et al.* 2007). This experience formed the basis for the leishmaniasis in east Africa platform (LEAP) 0104 trial, which was started in 2004 (final results are expected in early 2010) (ClinicalTrials.gov. c; Wakabi 2007). This phase 3 trial, which was done in Sudan, Ethiopia, Kenya, and Uganda, initially compared two monotherapy regimens—sodium stibogluconate (20 mg/kg for 30 days) and paromomycin sulphate (15 mg/kg for 21 days)—with the combination of both drugs at the same dose for 17 days (table 2) (ClinicalTrials.gov.c). In 2006, because of unexpectedly low efficacy with paromomycin monotherapy, the protocol was amended, and the dose of paromomycin was increased to 20 mg/kg in the second monotherapy group (Mudawi 2009). Whether the low efficacy related to drug resistance, differences in susceptibility, or pharmacokinetics is currently being investigated.

No large trials on other combination regimens have been done in Africa. Studies on miltefosine and amphotericin B as monotherapy are limited (Berman *et al.* 1998; Mueller *et al.* 2006; Mueller *et al.* 2008; Ritmeijer *et al.* 2006). A phase 2 study, which is due to start recruiting patients early in 2010, will assess the use of miltefosine (including pharmacokinetics) and combinations of liposomal amphotericin B plus either miltefosine or pentavalent antimonial (sodium stibogluconate) in an HIV-negative population (our unpublished data, Drugs for Neglected Diseases initiative). This study will provide important data on the efficacy of miltefosine within a standard clinical trial in east Africa, intends to facilitate drug registration

Table 2: Studies on combination therapy for visceral leishmaniasis in the Indian subcontinent and East Africa

	Study design	ClinicalTrials.gov registration	Country	Study period	Patients enrolled	Drug combinations studied	Definitive cure (95% CI) at 9 months in intention-to-treat analysis
Completed trials							
Sundar *et al.* [31]	Phase 2, randomised, non-comparative, group-sequential trial	NCT00370825	India	2008-08	181 adults: 45 each in groups A, C, D and E; 46 in group B	Group A: SD L-AmB 5 mg/kg alone; Group B: SD L-AmB 5 mg/kg followed by miltefosine 100 mg for 14 days; Group C: SD L-AmB 5 mg/kg followed by miltefosine 100 mg for 10 days; Group D: SD L-AmB 3.75 mg/kg followed by miltefosine 100 mg for 14 days; Group E*: SD L-AmB 5 mg/kg followed by miltefosine 100 mg for 7 days;	Group A: 91% (78-97%); Group B: 98% (87-100%); Group C: 96% (84-99%); Group D: 96% (84-99%); Group E: 98% (87-100%)
Planned or ongoing trials							
DNDi (VLCOMBO-07 trials)[33]	Phase 3, randomised, open-label, non-inferiority trial	NCT00696969	India, Bangladesh, and Nepal	2008-09 (India), 2009-10 (Bangladesh, Nepal)	624 adults and children†	Group 1: AmB 1 mg/kg every other day for 30 days; Group 2: SD L-AmB 5 mg/kg followed by miltefosine 2.5 mg/kg for 7 days; Group 3: SD L-AmB 5 mg/kg followed by paromomycin 15 mg/kg for 10 days; Group 4: miltefosine 2.5 mg/kg plus paromomycin 15 mg/kg for 10 days	..
Banaras Hindu University[32]	Phase 2, non-randomised, open-label, historical control, safety/ efficacy trial	NCT00371995	India	Ongoing	150 adults and children†	SD L-AmB 5 mg/kg followed by miltefosine 2.5 mg/kg for 14 days	..
TDR‡	Phase 2	..	Bangladesh	Planned	150†	SD L-AmB 5 mg/kg followed by miltefosine 2.5 mg/kg for 14 days	..
DNDi (LEAP0104A/B trial)[34]	Phase 3, randomised, open-label, active control, safety/ efficacy trial	NCT00255567	Kenya, Ethiopia, Sudan, and Uganda	2004-09 (LEAP0104A), 2007-10 (LEAP0104B)	1100 adults and children†	Active comparator group 1: SSG 20 mg/kg for 30 days; Group 2: paromomycin 15mg/kg (LEAP0104A) or 20 mg/kg (LEAP 0104B) for 21 days; § Group 3: SSG 20 mg/kg plus paromomycin 15mg/kg for 17 days	..
DNDi (VLCOMBO trial)¶	Phase 2, exploratory, randomised, open-label trial	..	Sudan and Kenya	Planned for 2009-10	189 adults and children; 63 in each group	L-AmB followed by miltefosine; L-AmB followed by SSG; Miltefosine 2.5 mg/kg for 30 days.	..

*Non-randomised group assigned when it had become apparent that all other regimens were effective. †Estimated. ‡B Arana, WHO Special Programme for Research and Training in Tropical Diseases, personal communication, Nov 3, 2009. §Due to poor outcomes on paromomycin 15 mg/kg in monotherapy in Sudan in LEAP0104A, the dose for paromomycin monotherapy was increased to 20 mg/kg in LEAP0104B. ¶Our unpublished data. AmB=amphotericin B. DNDi=Drugs for Neglected Diseases initiative. L-AmB=Liposomal amphotericin B. LEAP=leishmaniasis in east Africa platform. SD=single-dose. SSG=sodium stibogluconate. TDR=WHO Special Programme for Research and Training in Tropical Diseases. VLCOMBO=visceral leishmaniasis combination treatment.

in the region, and will also provide the first data on combination therapy based on liposomal amphotericin B. Because pentavalent antimonials are still highly effective in east Africa and have the additional advantage of being cheap, they indeed deserve further exploration in combination regimens when given for shorter duration and at lower total dose.

HEALTH-SYSTEM ISSUES

Access to and capacity of health systems

At present, major barriers exist in terms of access to diagnosis and care for visceral leishmaniasis, monitoring of treatment, and quality assurance of care. A recent study assessed the use of care by patients and delays in diagnosis and treatment in four endemic districts in India, Nepal, and Bangladesh (Mondal *et al.* 2009). In India, even poor people prefer to see a private medical practitioner for treatment of visceral leishmaniasis. In Bangladesh and Nepal, most patients rely on the public-health-care sector, although use of local pharmacists was high in Nepal (Mondal *et al.* 2009). Long delays in diagnosis and treatment were also reported. Overall, 23% of patients interrupted their treatment, mainly because of a lack of resources (67%) or side-effects (16%) (Mondal *et al.* 2009). In Africa, provision of visceral-leishmaniasis care has, until recently, mainly relied on non-governmental organisations. Diverse populations, ranging from semi-nomadic people to migrant workers, need to be reached in different contexts and environments (figure 2) (Desjeux 2004a; Den Boer *et al.* 2006; Desjeux 2001).

Therefore, the identification of an effective, well-tolerated, short regimen that can be given at the primary health-care level, needing little monitoring, and that is affordable both from the patient's and society's perspective would have a major public health impact on these populations. However, combination therapy might bring additional complexity in terms of logistics, service delivery, and programme monitoring. If not carefully considered and planned, combination therapy might actually increase the burden on the health-care system.

The combination of miltefosine and paromomycin might be an interesting option, because it could be given entirely within ambulatory care, and might even be suitable for delivery at the primary-care level. The weak health-care infrastructure would seem to argue against more complex intravenous administrations (e.g., amphotericin B or liposomal amphotericin B) and drugs that need more complicated laboratory and clinical monitoring (e.g., amphotericin B). The need to transport liposomal amphotericin B below 25°C could be another barrier for national programmes, although technological solutions exist that can guarantee transport of drugs below 25°C for 4—5 days. Steps could be taken to strengthen the supply chain of liposomal amphotericin B, and a single dose given at presentation could substantially ease the treatment protocol if the remaining drug could be given on an outpatient basis. Of note,

Figure 2: Visceral leishmaniasis happens in diverse contexts (Images from François Chappuis) Typical environment in Bihar, India (A). Seminomadic lifestyle in east Africa (B).

ambulatory treatment also needs sufficient capacity to assure good monitoring and follow-up. In cases in which miltefosine is used, an effective system to provide contraception also has to be considered because of the risk of teratogenicity. Despite extensive counselling on contraception, two cases of pregnancy were reported among the 227 women (≥12 years) treated in a phase 4 trial of miltefosine in India, with the conception date close to the exposure date (Bhattacharya *et al.* 2007). Fortunately, no birth anomalies were reported.

Cost-effectiveness

Thought must also be given to aspects of cost and cost-effectiveness of the various treatments available. In addition to the public health perspective, it is also important to consider the viewpoint of the household affected by visceral leishmaniasis. Studies found that the median total expenditure by the patient on visceral-leishmaniasis treatment was 1·2 times the annual per head income in Bangladesh (Sharma *et al.* 2006), 1·3 times in India (Meheus *et al.* 2006) and 1·1 times in Nepal (Rijal *et al.* 2006) Only limited data are available on the cost and cost-effectiveness of visceral-leishmaniasis treatment, and studies have mainly focused on monotherapy (Meheus *et al.* 2006; Rijal *et al.* 2006; Vanlerberghe *et al.* 2007). Olliaro and Sunder (Olliaro *et al.* 2009) recently calculated the cost of drugs on the basis of international drug prices and anthropometric data from a single health-care facility in Bihar, India. They found that paromomycin was the cheapest option (US$7·4 per patient) and that liposomal amphotericin B was the most expensive ($162—229 per patient) (Olliaro *et al.* 2009). Private

treatment with miltefosine cost $119 per patient, and $64—75 at the WHO-negotiated preferential price. However, these calculations did not include other direct or indirect costs, and might differ widely from country to country.

Combination therapies have the potential to reduce the cost to the public health system and patients by reducing the duration of treatment. This not only lowers the burden to the health system but also reduces the economic inactivity of patients. Preliminary findings on the cost-effectiveness of combination therapies in India, Nepal, and Bangladesh, showed combination therapies to be a viable alternative to monotherapies, with liposomal amphotericin B and paromomycin the best combination economically (Meheus *et al.* 2009). However, when we use the preferential drug price of miltefosine in the analysis, it seemed that miltefosine and paromomycin would be the preferred option from an economical perspective (our unpublished observations). No data exist on the cost-effectiveness of combination regimens in east Africa, but a study is due to start in Kenya, Ethiopia, and Sudan, with results expected in 2010 (Meheus F, unpublished).

Regulations and policy

Irrational drug use is a potential threat to the lifespan of any drug, and has probably contributed to the high level of treatment failure with pentavalent antimonials in Bihar, India (Sundar *et al.* 2001a). The unrestricted availability of antimonials in India resulted in widespread misuse by unqualified practitioners, leading to incomplete treatment courses. According to a survey of drug resistance in India, only 26% of patients were treated according to WHO guidelines, and patients often stopped treatment on their own initiative (Sundar *et al.* 1994). The high reliance on the private sector and local pharmacists in the Indian subcontinent even today highlight the need for tightened regulations on the modalities of visceral-leishmaniasis treatment, and for treatment to be made available at no cost (Den Boer *et al.* 2006; Sundar *et al.* 2005; Mondal *et al.* 2009). When policy makers opt for combination therapy, they should take measures to limit the use of monotherapy, particularly in incomplete courses. The fact that miltefosine is available in India without prescription or regulation on dispensed quantities is worrying, since this could facilitate the development of drug resistance (Sundar *et al.* 2005).

PREVENTION OF DRUG RESISTANCE

The problem of drug resistance in visceral leishmaniasis has been extensively reviewed elsewhere (Croft *et al.* 2006). Treatment failure can manifest as initial treatment failure (failure to clear parasites at the end of the treatment course) or relapse (reappearance of parasites after initial cure, usually within 6 months of follow-up). Although pentavalent antimonials have been

successfully used throughout the world for decades, poor treatment response (mainly due to initial treatment failure) has increasingly been reported since the 1980s from Bihar, India, with geographical and temporal clustering in several hyperendemic districts (Sundar 2001a; Peters 1981). Although treatment outcomes could initially be improved with higher total doses, the improvement was only temporary (Thakur *et al.* 1984; Thakur *et al.* 1988; Thakur *et al.* 1991). In subsequent reports, therapy failed in up to 60% of patients that were newly diagnosed (Sundar *et al.* 1995; Sundar *et al.* 1997; Sundar *et al.* 2000b). At the same time, misuse of the drugs was reported (Sundar *et al.* 1994). Increased treatment failure has also been reported in Nepal, in districts that neighbour Bihar (Rijal *et al.* 2003; Rijal *et al.* 2009). Although treatment failure can have several causes, including factors related to drug, host, and parasite, substantial evidence exists that acquired drug resistance is a key issue. Reduced drug sensitivity has been reported with *L donovani* strains from non-responsive cases in vitro (Lira *et al.* 1999; Laurent *et al.* 2007; Dube *et al.* 2005). Reduced susceptibility to pentavalent antimonials has also been reported with *L infantum* in both human beings and animals (Carrio *et al.* 2002; Carrio *et al.* 2001; Faraut-Gambarelli *et al.* 1997). In these studies, post-treatment isolates had reduced sensitivity compared with pretreatment isolates, supporting the notion of acquired drug resistance. However, more recent studies have reported less clear associations of in-vitro susceptibility and clinical outcomes, underscoring the need of improved and standardised methods (Rijal *et al.* 2009). The limited understanding of the mechanism of resistance towards pentavalent antimonials, and the shortcomings of drug sensitivity assays, make it difficult to predict the risk of acquired resistance in other regions or drugs and to assess the need for combination therapy to help prevent resistance. However, on the basis of the evidence, acquired drug resistance should be thought to be a potentially serious threat to visceral-leishmaniasis control, and comprehensive strategies should be developed, including the use of combination therapy (Bryceson 2001; Croft *et al.* 2006; Sundar 2001a; den Boer *et al.* 2009).

Rationale

For individual drugs, the ease with which resistance develops will mainly depend on the parasite burden, the probability of spontaneous development of resistance mutations, and the fitness cost associated with those mutations (Hastings 2001). The level and pattern of drug use in a population constitutes the selection force for the development of resistance, and intact host immunity is generally thought protective. The potency of the drug, therapeutic index, and pharmacokinetic properties of the drug also play a part (Hastings 2001). Combination therapy could delay resistance if two drugs with different modes of action and mechanisms of resistance are used. The combination of synergistic drugs is preferred, because if more effective replication can be inhibited, resistance is less likely during treatment.

For resistance prevention, both drugs should ideally have similar pharmacokinetics. If parasites always confront both drugs, the probability of the emergence of double-resistant parasites would be expected to be extremely rare (ie, the product of their individual per-parasite probabilities). A rapid elimination phase minimises the duration of subtherapeutic drug concentrations, which could provide an opportunity for amplification or selection of resistant parasites (Bryceson 2001; Hastings 2001; Stepniewska *et al.* 2008). In studies of malaria, the combination of one very active drug with a short half-life with a slower acting drug with a longer half-life to clear the remaining parasites has been explored as a way to shorten treatment duration and improve treatment compliance (Nosten *et al.* 2007). However, recent studies have focused on the terminal elimination phase of the second drug, which can act as a selective filter for resistant malaria parasites (Pongtavornpinyo *et al.* 2008; White 2004). Artemisinin resistance has recently been reported in Cambodia, but underlying reasons remain to be established (Noedl *et al.* 2008; Noedl *et al.* 2009; Dondorp *et al.* 2009). Finally, drugs can be combined to target different biological stages of the infectious agent. This has been done for tuberculosis and malaria, although the drugs are essentially targeted at preventing relapse and would only indirectly prevent or delay resistance.

Pharmacological considerations for combination therapy

Although the mechanisms of action and resistance remain poorly understood for all anti-leishmanial drugs in use (except amphotericin B), they are all thought to act on different targets (Alvar *et al.*2006). Recent findings from India suggest that field isolates from areas with high-level resistance to pentavalent antimonials show reduced sensitivity towards other anti-leishmanial drugs such as amphotericin B and miltefosine (Prajapati 2009; Kumar *et al.* 2009). However, true cross-resistance between the various drugs has not been reported so far. Several combinations have shown activity enhancement in animal experiments (Seifert *et al.* 2006; Seifert *et al.* 2009).

Clear differences in pharmacokinetics exist (Bryceson 2001). Miltefosine might be particularly vulnerable to the emergence of resistance, because of its narrow therapeutic index and long half-life, which has been estimated at around 7 days (Perez-Victoria *et al.* 2006; Berman *et al.* 2006). Recent data from patients with cutaneous leishmaniasis suggested a terminal half-life of 31 days, with miltefosine still detectable 5—6 months after the end of treatment (Dorlo *et al.* 2008). Resistant strains could be selected and amplified during this period because of subtherapeutic drug concentrations, either from relapsing patients, or from newly acquired infections (Perez-Victoria *et al.* 2006; Berman *et al.* 2006). If confirmed, this might have important repercussions on the risk of emerging resistance and on the duration of contraceptive measures.

Paromomycin has a short half-life (2—3 h in patients without visceral leishmaniasis), but has a low therapeutic index. Resistance can easily be induced in vitro (Maarouf *et al.* 1998), clinical resistance has been noted with its antibacterial use (Bryceson 2001; Davidson *et al.* 2009; Teklemariam *et al.* 1994), and some have argued against its use in monotherapy (Den Boer *et al.* 2006). Most of a pentavalent antimonial (about 99%) is eliminated within a few hours, followed by a slower elimination phase with a half-life of 76 h (Chulay *et al.* 1988). At least in east Africa, these drugs remain highly effective.

Amphotericin B could be thought less likely to induce resistance given its high efficacy and a relatively short half-life of 24 h (Bryceson 2001; Croft *et al.* 2006; Di Giorgio *et al.* 1999; Durand *et al.* 1998; Lachaud *et al.* 2009). Although resistance can been induced in vitro, clinical cases of amphotericin-B resistance have not been reported (Singh *et al.* 2001; Papadopoulou *et al.* 1998; Ouellette *et al.* 2004; Mbongo *et al.* 1998). Liposomal amphotericin B has a bioavailability in tissues for several weeks despite a relatively short plasma half-life (Gagneux *et al.* 1996; Adler-Moore *et al.* 2002). Given this long tissue half-life, a single dose of liposomal amphotericin B followed by daily administration of a second drug (eg, sodium stibogluconate, paromomycin, or miltefosine) would result in simultaneous exposure of the parasite to both drugs. The use of a single dose of liposomal amphotericin B (10 mg/kg) in monotherapy is being explored in India (ClinicalTrials.gov. d). Although this might be a simple and effective approach, concerns of resistance and cost should also be taken into account.

Compliance with treatment

Besides the intrinsic characteristics of the combination regimen, the use of and compliance to the regimen also affects the risk of drug resistance. All conventional monotherapies (apart from liposomal amphotericin B) need a long treatment duration (21—30 days), making compliance more challenging. This is of particular concern for treatment with miltefosine, the only oral drug, for which the risk of premature treatment interruption is high. Even in a phase 4 trial, 4·5% of patients were lost to follow-up before the end of treatment, and 14·5% were not available for assessment by 6 months after treatment (Bhattacharya *et al.* 2007). High default rates (up to 30%) were noted in a pilot study of miltefosine in India in ten districts (our unpublished data). Shorter treatment duration, particularly if the drug is also more tolerable, might help to increase compliance, as has been the case for patients on combination regimens for malaria (Bryceson 2001).

The lower costs to patients associated with shortened combination therapy could also improve access to and acceptability of visceral-leishmaniasis treatment. Some have suggested that the directly observed treatment strategy, which has been successfully used for tuberculosis,

might have a role in ensuring good compliance to miltefosine, although this will increase the indirect and direct costs (Croft *et al.* 2006; Sundar *et al.* 2007; Perez-Victoria *et al.* 2006). The elimination programme for visceral leishmaniasis in south Asia has opted for miltefosine as first-line drug, but will need to engage in the monitoring of clinical treatment outcomes and pharmacovigilance to ensure effective management (Sundar *et al.* 2007).

SPECIAL POPULATIONS: HIV COINFECTION

In east Africa, coinfection with HIV is a major challenge in the treatment of visceral leishmaniasis, with up to 30% of cases infected with HIV in some regions (Den Boer *et al.* 2006; Alvar *et al.* 2008; Lyons *et al.* 2003). This problem also seems to be on the increase in the Indian subcontinent (Mathur *et al.* 2006; Redhu *et al.* 2006). Because asymptomatic leishmania infections are thought to outnumber symptomatic infections, (Chappuis *et al.* 2007; Guerin *et al.* 2002) the dramatically increased risk of progression to visceral leishmaniasis after infection with HIV could lead to increased disease burden (Alvar *et al.* 2008), as has also been seen with tuberculosis (Harries 1990). Additionally, coinfection with leishmania and HIV is associated with a high mortality and a high rate of treatment failure and relapse with all visceral-leishmaniasis drugs (Alvar *et al.* 2008; Ritmeijer *et al.* 2006; Ter Horst *et al.* 2008; Ritmeijer *et al.* 2009). The efficacy of combination therapy for coinfection with leishmania and HIV has not yet been studied in a controlled trial.

Although widespread use of antiretroviral therapy has resulted in large reductions in the incidence of visceral-leishmaniasis—HIV coinfection in southern Europe, it seems to be only partly protective against relapses (Alvar *et al.* 2008; Ter Horst *et al.* 2008). Patients with incurable disease (who present with relapse or post kala-azar dermal leishmaniasis) could serve as a reservoir for the development and spread of drug-resistant strains, particularly because such patients seem to be more infectious (Molina *et al.* 2003). To increase efficacy, combination therapy might be particularly relevant for coinfected patients to prevent resistance, because repeated exposure to single anti-leishmanial drugs will facilitate the emergence of resistant parasites. Even if relapses cannot be prevented, combination therapy might preserve drug sensitivity. Although one study reported decreased sensitivity towards amphotericin B after several treatment courses in individuals infected with HIV (Di Giorgio *et al.* 1999), this has not been confirmed (Durand *et al.* 1998; Lachaud *et al.* 2009).

Given the overall poor treatment outcomes, patients infected with HIV are most likely to need a different first-line therapy from patients not infected with HIV, at least in terms of treatment duration. However, none of the planned or continuing phase 3 trials include patients infected with HIV. Whether secondary prophylaxis could prevent relapses remains unclear. WHO does not recommend secondary prophylaxis in foci of anthroponotic visceral leishmaniasis (WHO 2007).

FUTURE PERSPECTIVES

Although the principle of combination therapy is generally accepted, the rationale for the choice of the drugs in such combination regimens is still under debate (Bryceson 2001; Croft *et al.* 2006; Den Boer *et al.* 2006). Several combinations have been taken forward in clinical studies, which will most likely provide us with several efficacious treatment options in the near future. However, it remains to be defined what exactly we should expect from combination therapy, and which factors will be important in selecting a specific therapy within a given context.

The current or planned clinical trials on combination therapy for visceral leishmaniasis in Asia and Africa will essentially provide data on safety and efficacy of the different regimens. Whereas drug—drug interactions, both in terms of pharmacokinetics and toxicity, have been prime considerations in the development of combination therapy for other infectious diseases, only limited data on anti-leishmanial drugs are available. Since the leishmania parasite targets reticulo-endothelial cells within specific organs, factors such as tissue distribution and uptake into macrophages of the individual components within combination therapy might also be relevant (Seifert *et al.* 2006). Whereas reduced toxic effects with combination therapy could possibly improve drug tolerance, because of reduced total doses of the individual compounds, increased toxicity could also be possible. Although the available data from animal and human studies seem reassuring, more studies to address these issues should be done. At least some of the combination studies that have been planned by the Drugs for Neglected Disease initiative will include pharmacokinetic substudies (our unpublished data).

Forthcoming results of clinical trials will not address the future public health benefits of combination therapy nor how it should be applied in field settings. Particularly, data from east Africa on liposomal amphotericin B suggest that many patients present with advanced and complicated visceral leishmaniasis and that perhaps relatively intensive treatment might be needed for cure (Berman *et al.* 1998; Collin *et al.* 2004; Mueller *et al.* 2007; Seaman *et al.* 1995). Because these patients are generally not included in phase 3 trials, these issues should be further addressed in field studies. Even in the recently reported phase 4 trial of miltefosine

in India, 10% of patients were excluded (Bhattacharya *et al.* 2007). More research on safety issues also needs to be done.

It will take several years before sufficient clinical data will be available and combination therapy will be effectively implemented in the field. In the meantime, care should be taken to minimise the development of resistance to the individual drugs. Compared with miltefosine, liposomal amphotericin B might be a more cautious option, because substantial resistance towards liposomal amphotericin B is unlikely to happen when used as large-scale monotherapy for a few years. Recent data from India on the use of standard dose of liposomal amphotericin B in operational settings have shown excellent treatment outcomes (Lima 2009).

Most likely, regional factors will play an important part in deciding on the best combination therapy for a particular area, region, or country. Regional differences in natural or acquired drug resistance or pharmacokinetics should be considered. Differences in nutritional status and prevalence of coinfections such as HIV and tuberculosis might also determine the choice of combination therapies. Finally, regional factors will also determine which combination could be made available with the largest coverage and compliance in a sustainable and stable matter, and which delivery model would be most cost-effective.

KEY QUESTIONS AND CHALLENGES

Trial data of several combination therapies will become available over the next few years, and should address some of the issues that have been discussed. However, many questions and challenges remain (panel). Whereas combination therapy aims to increase the lifespan of available drugs, this could also lead to rapid loss of two therapeutic options, if not applied in a controlled and regulated way. Care should be taken to ensure that the increased complexity of the logistics of combination therapy does not hamper effective implementation. The evidence base for combination therapy should be regularly re-assessed within each specific context.

How an effective treatment strategy should be integrated within the private and public-health sectors and how this determines the choice of (combination) regimen are unclear. Without increased access to and capacity of health care, both in terms of diagnosis and treatment, the overall effect of any (combination) therapy will be small. Efforts to reduce transmission also need to be addressed. The factors that affect the acceptability of visceral-leishmaniasis care and how to improve it will also need to be taken into account.

Close monitoring of combination therapy will be important at several levels. Programme monitoring will allow assessment of the overall effect, to identify barriers, and to supervise

the correct implementation and use of combination therapy. Systems should also be put in place to detect counterfeit drugs or illegal drug supply. In areas with high prevalence of HIV or tuberculosis, close links and integration with the national programmes will be pivotal.

Panel: Key questions and challenges

- Key questions and challenges
- To what extent are the available anti-leishmanial drugs threatened by the development of drug resistance when used in monotherapy?
- Will combination therapy effectively delay acquired drug resistance and how is this best achieved?
- How do we set up an effective surveillance system to detect the development of acquired drug resistance?
- What will be the field efficacy of combination therapy?
- How do we set up a pharmacovigilance system?
- How do we assure good compliance with ambulatory treatment?
- Is there a need for a (daily) directly observed therapy strategy for miltefosine?
- How do we effectively implement a combination therapy strategy and, at the same time, increase access to care and diagnostic and therapeutic capacity?
- What is most cost-effective and feasible delivery model for visceral-leishmaniasis care in a specific setting?
- How do we regulate and control prescription of combination therapy, and how do we detect or prevent extra-legal drug use?
- What is the place of the private health care in visceral-leishmaniasis treatment?
- Do public—private partnerships have a place in the provision of care and treatment for visceral leishmaniasis?

Although reliable programme data can show the effectiveness of treatment regimens in use, they do not allow emerging resistance to be traced at an early stage. Parasite drug susceptibility should be monitored within surveillance systems, as being deployed for tuberculosis, malaria, and HIV. Because in-vitro susceptibility assays used at present have substantial limitations, further optimisation and standardisation remain necessary (Croft 2001; Rijal *et al.* 2007). The development of molecular markers of resistance, as pursued by several research groups, could be a way forward in the long run if also made available in endemic countries (Perez-Victoria *et al.* 2006). Moreover, visceral-leishmaniasis therapies carry a substantial risk of toxic effects, and there are is obviously no long-term experience with combination therapy. Particularly if miltefosine is to be used on a large scale, problems related to teratogenicity or other unknown side-effects should be traced at an early stage.

Whether combination therapy also has an important place in the prevention of drug resistance, and how this is best achieved, will only be known in the long run. Aiming for a combination therapy that is highly effective, widely accessible, affordable, and with high rates of compliance should probably be the priority.

Search strategy and selection criteria

Articles cited in this Review were obtained through searches of PubMed or Medline for papers published up to June 1, 2009, with terms including, but not restricted to, the following combinations: "visceral leishmaniasis", "treatment", "combination therapy", "safety", "efficacy", "cost", "cost-effectiveness", "resistance", "compliance", "health system", and "human immunodeficiency virus". The search was limited to English. Reference lists of these articles were then searched to identify other relevant publications. Clinical trial websites were verified, and experts in clinical research in visceral leishmaniasis were contacted for information on planned or ongoing trials. Abstracts of recent international conferences on infectious diseases were also reviewed. We structured our Review around the following criteria: efficacy and safety, health-system aspects (feasibility, cost-effectiveness and regulations), potential for drug resistance, and use in special populations.

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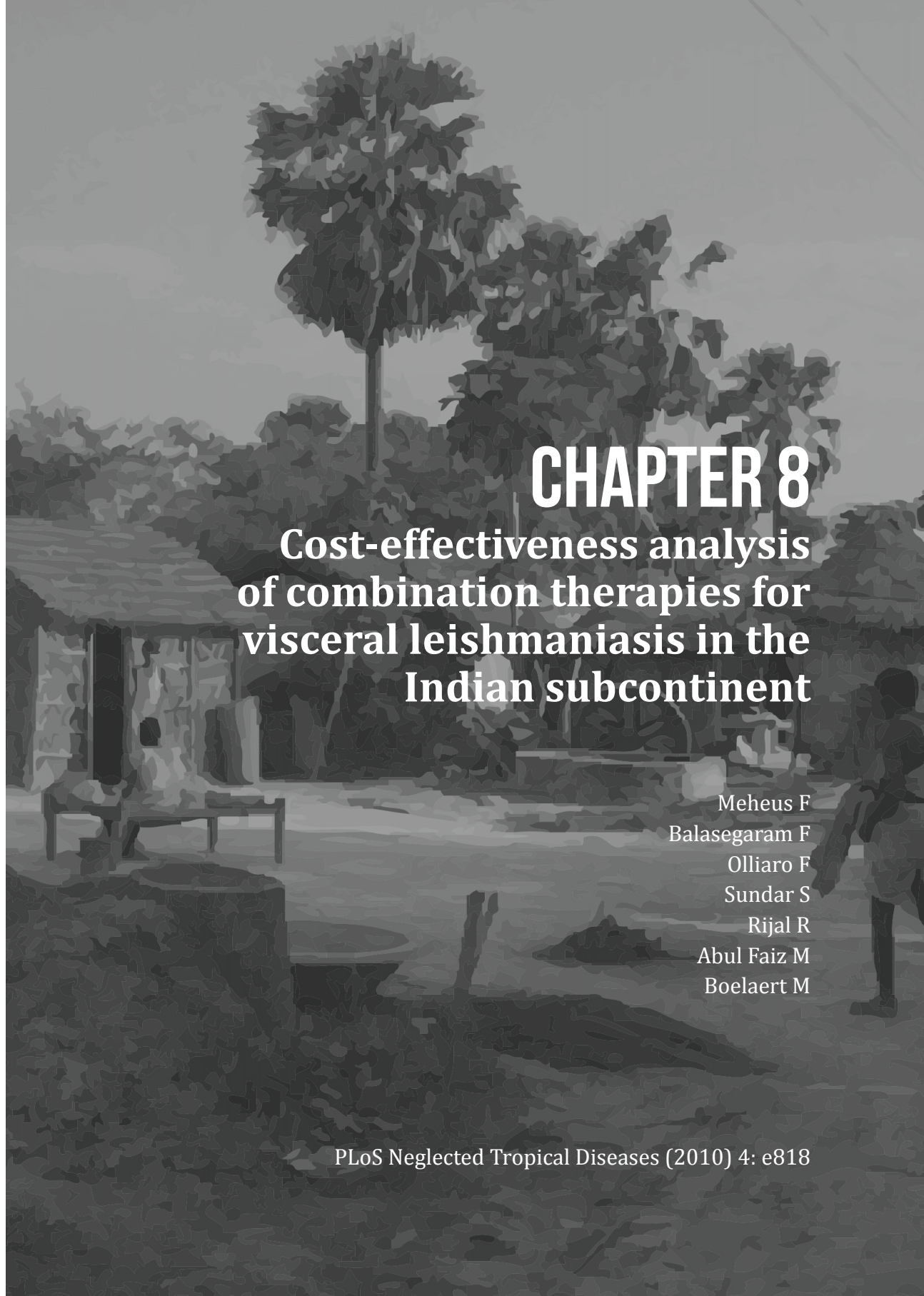

CHAPTER 8

Cost-effectiveness analysis of combination therapies for visceral leishmaniasis in the Indian subcontinent

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ABSTRACT

Background

Visceral leishmaniasis is a systemic parasitic disease that is fatal unless treated. We assessed the cost and cost-effectiveness of alternative strategies for the treatment of visceral leishmaniasis in the Indian subcontinent. In particular we examined whether combination therapies are a cost-effective alternative compared to monotherapies.

Methods and findings

We assessed the cost-effectiveness of all possible mono- and combination therapies for the treatment of visceral leishmaniasis in the Indian subcontinent (India, Nepal and Bangladesh) from a societal perspective using a decision analytical model based on a decision tree. Primary data collected in each country was combined with data from the literature and an expert poll (Delphi method). The cost per patient treated and average and incremental cost-effectiveness ratios expressed as cost per death averted were calculated. Extensive sensitivity analysis was done to evaluate the robustness of our estimations and conclusions. With a cost of US$92 per death averted, the combination miltefosine-paromomycin was the most cost-effective treatment strategy. The next best alternative was a combination of liposomal amphotericin B with paromomycin with an incremental cost-effectiveness of $652 per death averted. All other strategies were dominated with the exception of a single dose of 10mg per kg of liposomal amphotericin B. While strategies based on liposomal amphotericin B (AmBisome) were found to be the most effective, its current drug cost of US$20 per vial resulted in a higher average cost-effectiveness. Sensitivity analysis showed the conclusion to be robust to variations in the input parameters over their plausible range.

Conclusions

Combination treatments are a cost-effective alternative to current monotherapy for VL. Given their expected impact on the emergence of drug resistance, a switch to combination therapy should be considered once final results from clinical trials are available.

INTRODUCTION

Despite their toxicity, pentavalent antimonials are still widely used as first line treatment for visceral leishmaniasis (VL) except in the Indian subcontinent where emerging drug resistance in Bihar State in India (Sundar *et al.* 2000b) and Nepal (Rijal *et al.* 2003) required a change in drug policy. Current therapeutic options include amphotericin B deoxycholate (AmB), liposomal amphotericin B (L-AmB), miltefosine (MF) and paromomycin (PM). The VL elimination initiative launched in 2005 by the governments of India, Nepal and Bangladesh adopted miltefosine as the first line treatment (Sundar *et al.* 2008; WHO 2005). More recently paromomycin was registered in India as a first line regimen for VL (Sundar *et al.* 2007). However, parasite resistance to MF and PM can be induced experimentally (Seifert *et al.* 2003) and is expected to emerge naturally if optimal adherence cannot be ensured (Bryceson 2001). The World Health Organization has recommended the use of liposomal amphotericin B (L-AmB) based on high efficacy and safety (Bern *et al.* 2006). While the development of resistance has not yet been demonstrated for AmB and L-AmB, practicalities (requirements for cold chain and intravenous perfusion) and the high drug cost have so far delayed its adoption as first line treatment. As there are no new compounds for VL expected to come to the market in the near future, policies that delay or prevent the emergence of resistance to the currently available drugs are therefore required. A possible strategy that has been successfully used for malaria and tuberculosis is the use of combination therapies (van Griensven *et al.* 2010). Combination therapies may also increase tolerability, reduce treatment duration and possibly (direct and indirect) costs.

Phase III clinical trials of combination therapies for VL are currently underway testing the efficacy and safety of several combinations and results are expected in 2010 (Clinicaltrial.gov, Identifier: NCT00696969; for more information see http://clinicaltrials.gov/). Choices in VL drug policy should be based on efficacy, safety as well as the cost of treatment, the process of patient management and the factors influencing treatment effectiveness, such as adherence. The latter factor is particularly important as some regimens (e.g. injectables) are likely to lead to higher compliance than others.

The objective of the present study was to assess the cost-effectiveness of various treatment options for VL, and in particular to evaluate whether combination therapies are a cost-effective alternative to monotherapy.

METHODS

Description of alternatives

We considered 10 alternative treatment strategies: (1) all monotherapies that are either already implemented or under consideration and (2) combination therapies currently included in a phase III clinical trial (See table 1). AmB has infusion-related and delayed toxicities (e.g.nephrotoxicity) (Sundar *et al.* 2004) and requires prolonged parenteral administration and hospitalisation. MF has the advantages of an oral drug but causes serious adverse events in 2–3% of patients (Bhattacharya *et al.* 2007) , has a long half-life and is possibly teratogenic. It can thus not be used in pregnant women and women in child-bearing age should accept contraception over the treatment period and up to two months after (Sundar *et al.* 2004a). PM seems a safer option - though phase IV results are still pending - and relatively cheap, but requires intramuscular injections. L-AmB is highly efficacious (>90%) even in a single dose of 5–10 mg/kg in India (Sunder *et al.* 2002b; Sunder *et al.* 2003b; Sundar *et al*. 2010) and is safe, but it is expensive despite a preferential price offered by the manufacturer to the public sector and requires an efficient cold chain. All of the other more "affordable" monotherapies listed above (MF, PM, AmB) require prolonged treatment which is problematic in very poor population groups that are dependent on daily labour and pay much out-of-pocket.

Table 1: Overview of treatment strategies included in decision analysis model.

Strategy	Drug	Length of treatment (days)
A	L-AmB (5MK) + Miltefosine (50/100 MD)	8
B	L-AmB (5MK) + Paromomycin sulphate (15 MKD)	11
C	Miltefosine (50/100 MD) + Paromomycin sulphate (15 MKD)	10
D	SSG (20 MKD) + Paromomycin sulphate (15 MKD)	17
E	Miltefosine (50/100 MD)	28
F	Paromomycin sulphate (15 MKD)	21
G	Amphotericine B deoxycholate (1 MK eod)	30
H	L-AmB10 (10 MK)	1
I	L-AmB20 (5 MKD)	4
J	Sodium Stibogluconate (20 MKD)	30

L-AmB : Liposomal Amphotericine B
MK = mg/kg single dose; MD = mg per day; MKD = mg/kg body weight per day
Miltefosine is given at 50 mg/ day if body weight is <25 or 100 mg if body weight ≥25 kg per day

Decision model

A decision tree model, depicted in figure 1, was developed using TreeAge Pro Suite v2009 (TreeAge Software Inc., Williamstown, MA, USA) to determine the outcome of a single confirmed VL patient receiving first-line treatment at a primary health care facility. The outcome was expressed in terms of number of deaths averted and we assumed a case-fatality rate of 100% in the absence of treatment. For each treatment strategy, the patient either adheres or does not. Those adhering are either cured or experience treatment failure. Patients not adhering to treatment were considered lost to follow-up and we assigned a value of 0 deaths averted. For strategies combining L-AmB with MF or PM, we assigned a value of 0.91 in case of non-adherence since patients will have received a single dose of 5mg/kg of L-AmB (with 91% cure rate) (Sundar *et al*. 2008b; Sundar *et al*. 2001) on the first day before they are lost to follow-up. Since MF is contraindicated in pregnant and breastfeeding women or women in child bearing age because of its potential teratogenic effect, the path for strategies including MF is different from those without MF. MF can only be given if the patient accepts the use of contraceptive measures during treatment and up to two months after completion of treatment. This is captured in the model by including an additional probability representing the contraceptive prevalence in the community. We calculated the cost per case treated and the average and incremental cost-effectiveness ratios (ICERs) expressed as the cost per death averted. The ICER represents the additional cost to gain an additional unit of effectiveness (i.e. one additional death averted) and is calculated by dividing the incremental cost of a given strategy by its incremental effectiveness compared to the previous not dominated strategy.

Furthermore we assumed in the baseline analysis the patient to be hospitalized for at least one day for all strategies; for treatment with AmB the patient is hospitalized for the entire duration of treatment (30 days) as this drug needs to be given under close supervision. Strategies with PM and SSG are provided on an outpatient basis whereby the patient visits the health facility daily to receive the intramuscular injection. In the case of treatment with MF, the patient visits the health facility weekly to receive a 1-week supply of the drug. We also assumed patients to undergo weekly routine laboratory investigations (blood count, liver and renal function tests), a pregnancy test for women in child-bearing age and an HIV test.

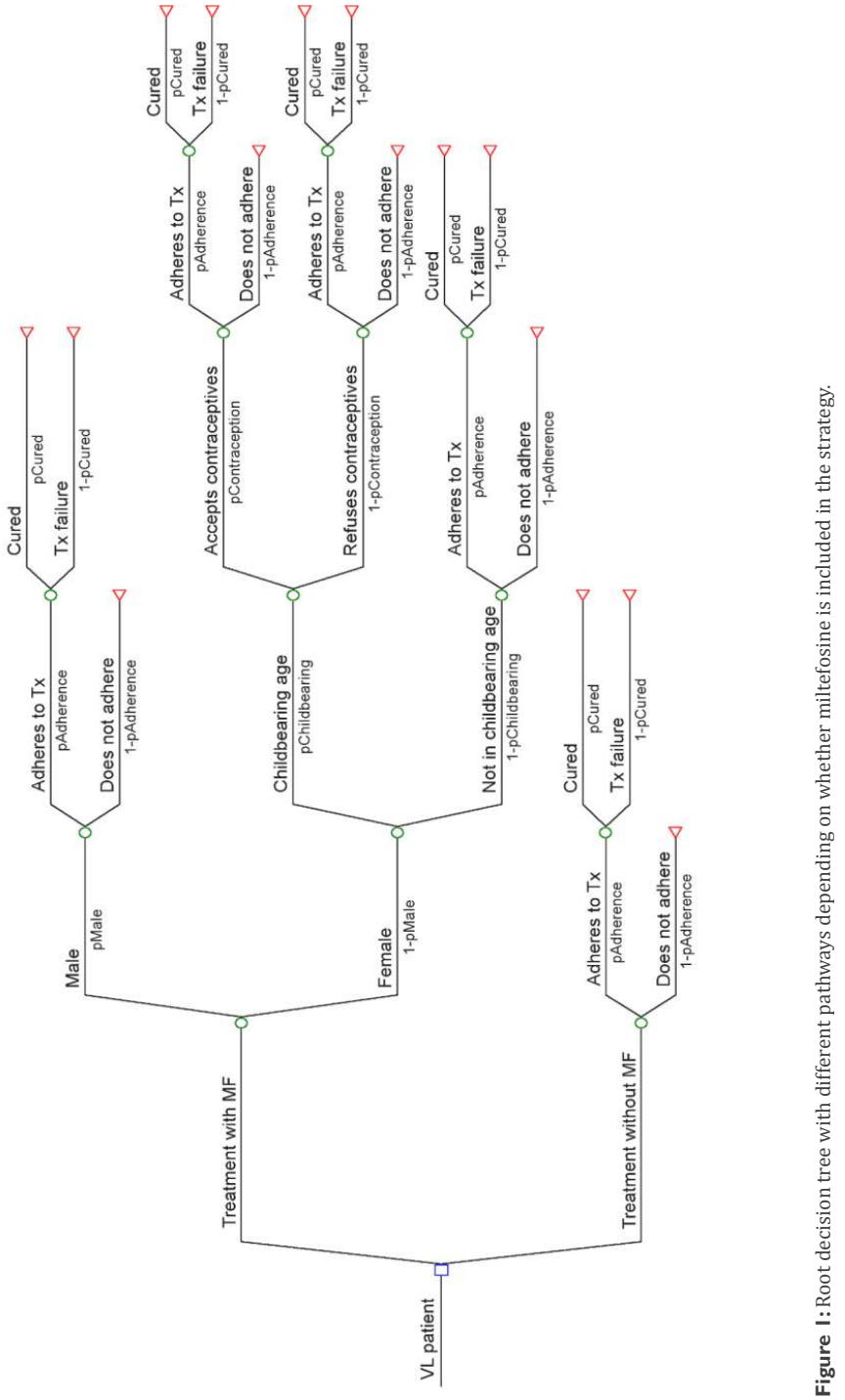

Figure 1: Root decision tree with different pathways depending on whether miltefosine is included in the strategy.

Probabilities

The probabilities used in the model are shown in table 2. These consist of a most plausible value used in the baseline analysis and the range used in the sensitivity analysis. We used anthropometric data from a sample of 1496 patients attending a dedicated VL treatment centre in Muzaffarpur, Bihar (India) (Olliaro & Sundar 2009) to derive probabilities on patient characteristics (age, weight and sex). Other values were obtained from expert opinion and published literature. To derive the probabilities related to efficacy and compliance for therapies that are still in clinical trials, we consulted a group of VL experts in an adapted Delphi process to reach consensus after two consultation rounds. In the first round seven clinical experts were presented with a survey asking for efficacy and compliance values for all treatments. Subsequently results from this round were summarized and presented to the experts to revise their earlier answers (round 2). For estimates derived from the literature, we used data from clinical trials using the pooled estimate in the baseline analysis and used the minimum and maximum for sensitivity analysis. All estimates represent definite cure rates defined as the absence of VL at 6 month follow-up; failure, relapse and fatal toxicity are included in the estimates. While minor side effects, such as diarrhoea and vomiting may occur, we did not consider these in the model since they do not hamper the completion of treatment.

We assumed treatments of short duration (strategies A, B, C, H and I) to result in high compliance. Similarly, treatment with AmB was assumed to lead to high compliance since treatment is provided on an inpatient basis. On the other hand, patients receiving MF for 28 days receive a 1-week supply of drug at a time for self-administration and compliance is anticipated to be lower than for the other strategies, consistent with findings from a miltefosine phase IV study by Bhattacharya et al (2007) (Bhattacharya *et al.* 2007) where the final cure rate was 82% on intent-to-treat analysis due to the high losses to follow-up.

Costs

Table 3 summarizes cost estimates presented in 2008 US dollars (US$). Costs were obtained from primary data collected in 2008 using an ingredients based approach (i.e. collecting information on quantities and prices) and supplemented by data from the literature. We adopted a societal perspective including both provider and patient costs. These costs consist of direct medical costs (e.g. antileishmanial drugs, administration kits (intravenous sets, syringes and needles), laboratory investigations and the cost of hospitalization and outpatient care); direct non-medical costs (transportation to/from the health facility) and indirect costs representing the loss of income to the patient. The cost of drugs was obtained from WHO, Médecins sans Frontières (MSF) and the Institute of One World Health (iOWH). The cost of L-AmB was US$ 20 per 50 mg vial (AmBisome, Gilead, USA), MF (Impavido previously Zentaris, Germany, now

Table 2: Model parameters (a)

Variable	Likeliest (base)	Minimum	Maximum	Source
Demographic parameters of sample (%)[b]				
Women in the sample	39	30	50	Olliaro & Sundar 2009; Thakur *et al.* 2000b
Women of childbearing age (15-49 yrs) of all VL	17	10	35	Olliaro & Sundar 2009; Thakur *et al.* 2000b
Patients weighing less than 25 kg	41	20	60	Olliaro & Sundar 2009; Thakur *et al.* 2000b
Children (0-14 years)	51	25	75	Olliaro & Sundar 2009; Thakur *et al.* 2000b
Adults (15-80 years)	49	25	75	Olliaro & Sundar 2009; Thakur *et al.* 2000b
Drug efficacy (%)				
L-AmB + MF	95	90	99	a; Sundar *et al.* 2008b
L-AmB + PM	95	90	99	a
MF + PM	95	91	99	a
SSG + PM	90	85	98	a; Thakur *et al.* 2000b; Thakur *et al.* 1992
MF	94	82	94	Sundar *et al.* 2002a; Thakur *et al.* 2000b; Bhattacharya *et al.* 2004; Sundar *et al.* 2003a; Sundar *et al.* 2000a
PM	94	89	95	a; Sundar *et al.* 2007; Jha *et al.* 1998; Sundar *et al.* 2009; Thakur *et al.* 2000a
AmB	97	96	99	Sundar *et al.* 2007; Sundar *et al.* 2004; Sundar *et al.* 2002a; Thakur *et al.* 1999
L-AmB10	95	93	98	a; Sundar *et al.* 2010
L-AmB20	95	93	99	a; Thakur 2001
SSG	70	35	93	Sundar *et al.* 2000b; Rijal *et al.* 2003; Thakur *et al.* 2000b; Jha *et al.* 1998; Thakur *et al.* 2000a; Thakur & Narayan 2004; Thakur *et al.* 2008; Thakur *et al.* 1998; Sundar *et al.* 1997

Table 2: Model parameters (b)

Variable	Likeliest (base)	Minimum	Maximum	Source
Compliance to treatment (%)				
L-AmB + MF	95	80	97	a
L-AmB + PM	95	85	97	a
MF + PM	95	80	97	a
SSG + PM	83	75	90	a
MF	80	60	90	a; Bhattacharya *et al.* 2007
PM	85	75	90	a
AmB	90	80	90	a
L-AmB10	100	-	-	a
L-AmB20	98	95	100	a
SSG	75	60	90	a
Contraceptive prevalence (%)	55	30	70	a; WHO-WHOSISc

[a] Estimates obtained from expert opinion (Delphi method).

[b] Baseline values were varied ±50% in sensitivity analysis

[c] Average of figures reported for Bangladesh 58.1% (2004); India 56.3% (2006); Nepal 48.0% (2006)

Paladin, Canada) US$ 1.41 per 100 mg capsule (or US$ 79 per blister of 56 capsules; the market price of US$ 2.68 per capsule was used as the maximum value in the range), PM US$ 0.71 per 1000 mg ampoule (Gland Pharma Ltd, India), AmB US$ 1.90 per mg vial (Combinopharm, Spain) and SSG US$ 8.25 per vial (Albert David, India). The average drug cost per patient for each strategy was estimated using the anthropometric database. The baseline cost of laboratory investigations includes the cost of equipment, supplies, reagents, the technician's time and indirect laboratory costs (i.e. overhead costs obtained through step-down costing) and is an average cost calculated at a VL treatment centre in India (Muzaffarpur) and a health facility in Nepal (Dharan). The range consists of prices charged to patients at public health facilities and private laboratories. The unit cost per inpatient bed-day and outpatient visit was estimated at a charitable clinic in India (Meheus *et al.* 2006). The maximum value used in the range was derived from WHO-CHOICE estimates for the South Asian region (Mulligan *et al.* 2003). Average income was estimated with the human capital approach and was estimated at US$ 1.48 per day Meheus *et al.* 2006). We assumed that the patient was not able to work for the full duration of treatment. Indirect costs were varied from 0 (i.e. excluding indirect costs) to twice the baseline value in sensitivity analysis. Costs related to diagnosis of VL were not included in the analysis since these are the same for all strategies.

Table 3: Cost estimates of each treatment strategy per patient treated (US$ 2008).

Strategy	Drug cost	Other direct medical[1]	Non-medical & indirect	Total cost[2]
L-AmB+MF	95.7	14.8	12.8	123.4
L-AmB+PM	87.1	20.5	25.3	132.9
MF+PM	29.5	19.5	23.8	72.9
SSG+PM	45.1	29.9	43.6	118.6
MF	62.8	22.0	45.4	130.2
PM	14.9	30.6	51.1	96.6
AmB	20.9	131.6	45.4	197.9
L-AmB10	140.0	11.0	2.5	153.4
L-AmB20	280.0	24.7	6.9	311.6
SSG	57.8	40.7	73.4	171.8

[1] Includes costs of contraceptives, administration (intravenous kits, solutions, syringes), laboratory investigations. It also includes the cost per inpatient bed-day and outpatient visit obtained.
[2] Total costs of strategies with MF in this table do not include cost of AmB given to women in childbearing age that refuse to take contraceptives and are therefore different from total costs mentioned in table 4.

All costs were adjusted to the 2008 national currency of each country using the consumer price index and converted to US dollars using the exchange-rate prevailing at that time.

Sensitivity analysis

To examine the uncertainty around variables and how these affect the outcome and conclusions of our study, we conducted a series of one-way and two-way sensitivity analyses. Since values for drug efficacy and compliance were largely based on expert opinion we varied the values of these variables over the plausible range specified in table 2. On the cost side, we examined the impact of changing drug prices. While the price of most drugs, such as PM or AmB is unlikely to change much in the future given their low cost, there is uncertainty with regard to the pricing of MF and L-AmB. MF was recently acquired by Paladin Labs Inc., Canada from Zentaris, and it is at the time of writing unclear if the current negotiated differential prices will be maintained. For L-AmB, despite substantial price reductions, the cost per vial remains high and there may be room for further price reductions. To test the robustness of our results we (i) varied each drug cost separately; (ii) conducted a threshold analysis to determine at what price level strategies with L-AmB become the most cost-effective; and (iii) conducted a two-way sensitivity analysis of the price of MF and L-AmB. We also varied the unit cost per inpatient bed-day and outpatient visit. Finally, we examined the impact of indirect costs. In

the baseline analysis we assumed the patient would not be able to work for the full duration of treatment. But in practice, with effective treatment, patients may already feel better after a week of treatment and resume their activities. The indirect cost of strategies with longer treatment duration could therefore be overestimated. In addition the inclusion of indirect costs is a controversial issue, mainly due to the valuation method (Tan Torres *et al.* 2003). We therefore looked at the impact of indirect costs by (i) limiting productivity losses to a week, and (ii) excluding indirect costs from estimations.

RESULTS

Baseline analysis

Table 4 shows the expected cost and effectiveness for each treatment strategy using baseline values. Strategies were ranked in ascending order of costs. Strategies based on treatment with L-AmB, either used as a single agent or in combination, were found to be more effective compared to other strategies with a single dose of 10mg/kg of L-AmB (strategy H) being the most effective and averting 95% of deaths. This high effectiveness of strategies with L-AmB is explained by the combination of high drug efficacy and a short treatment duration resulting in high expected compliance to treatment. After strategies with L-AmB, the next best alternative is the co-administration of MF and PM (strategy C) averting 90% of deaths. Monotherapies with either SSG (strategy J) or MF (strategy E) had the lowest effectiveness. For SSG this is due to the low efficacy of the drug and for MF due to the low expected treatment compliance.

Table 4: Results in the baseline analysis.

Strategy	Cost (C)	Incremental Cost*	Effectiveness (E)	Incremental Effectiveness*	C/E	Incremental C/E (ICER)**
MF + PM	82.5		0.900		92	
PM	96.6	14.1	0.799	-0.101	121	(Dominated)
SSG + PM	118.6	36.1	0.747	-0.153	159	(Dominated)
L-AmB + MF	129.1	46.6	0.942	0.042	137	1123**
L-AmB + PM	132.9	3.8	0.948	0.006	140	652
MF	135.4	2.5	0.761	-0.186	178	(Dominated)
L-AmB 10	153.4	20.6	0.950	0.002	162	8224
SSG	171.8	18.4	0.525	-0.425	327	(Dominated)
AmB	197.9	44.5	0.873	-0.077	227	(Dominated)
L-AmB 20	311.6	158.2	0.949	-0.001	328	(Dominated)

The least costly treatment is the co-administration of MF with PM (strategy C) with a cost of $72.9 per patient treated. The cost per patient treated for the other strategies varied from $96.6 (strategy F) to $311.6 (strategy I). The breakdown of costs for each strategy is shown in table 3. The drug cost as a proportion of total costs is the highest for strategies including L-AmB. The price of a 50mg vial of L-AmB at the time of this analysis was $ 20 and is the most expensive VL drug. Obviously, the higher the dosage, the more expensive the treatment. For example the drug cost of strategy I (20mg/kg of L-AmB for 4 days) is $280. The highest "other" direct medical costs were found for strategies requiring prolonged treatment, with treatment on an inpatient basis (strategy G) being the most expensive. Similarly, strategies with long treatment duration and/or requiring many visits to the health facility for administration of the drug have the highest indirect cost.

Cost-effectiveness results are illustrated in figure 2 and reported in table 4. All treatment strategies on the left of the line are dominated by strategies C, B and H because they are equally or less effective, and either cost more (strong dominance) or have an incremental cost-effectiveness ratio that is higher than the next more effective strategy (extended dominance). The incremental cost, incremental effectiveness, cost-effectiveness ratio (CER) and incremental CER without the dominated strategies are reported in table 5.

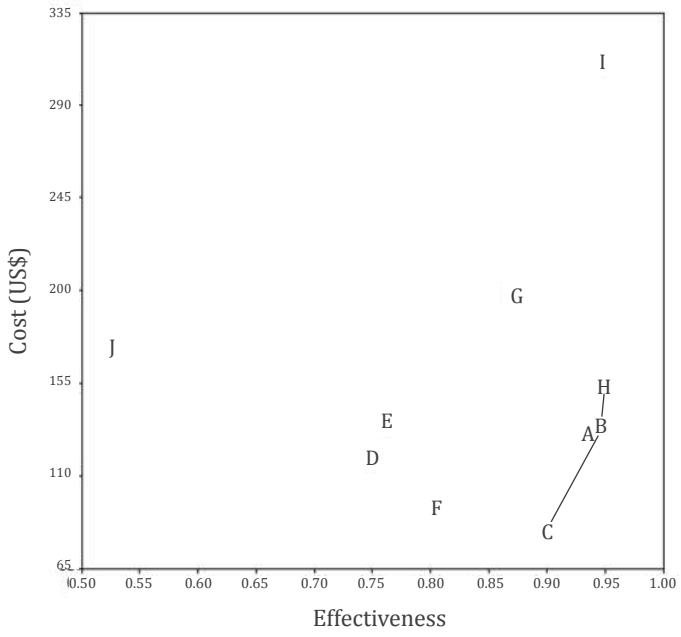

Figure 2: Cost-effectiveness ratio (US$/death averted) of 10 treatment strategies for visceral leishmaniasis.

Line CBH shows dominance. All strategies left of this line are dominated by C, B and H, meaning they are equally or less effective and more costly.

Table 5: Baseline results without dominated options (simple or extended).

Strategy	Cost (C)	Incremental Cost*	Effectiveness (E)	Incremental Effectiveness*	C/E	Incremental C/E (ICER)**
MF+PM	81.9		0.900		91	
L-AmB+PM	132.9	51.0	0.948	0.047	140	1079
L-AmB10	153.4	20.6	0.950	0.002	162	8224

The most cost-effective strategy appears to be strategy C whereby MF and PM are co-administered. Compared with this strategy, the next most cost-effective strategy is the combination of L-AmB with PM (strategy B), followed by a single dose of 10mg/kg of L-AmB (strategy H). While L-AmB combined with MF (strategy A) is more effective than strategy C, it is also more costly and has a higher (incremental) cost-effectiveness ratio that the next best alternative (i.e. strategy B). In other words the additional cost per death averted is lower for strategy B than strategy A.

Sensitivity analysis

The study findings were robust to most changes in the input variables. Varying the values of the drug efficacy and compliance over their plausible range did not affect the ranking of strategies. A sensitivity analysis assuming that all non-adherent patients would effectively be cured did not change the ranking of strategies either. With regard to costs, while varying the price of MF did not alter results, the cost-effectiveness results were sensitive to a change in the price of L-AmB. If the price of a vial is decreased by more than 51% to less than $ 9.8, then strategy H becomes the most cost-effective strategy. The relationship between the price of MF and the price of L-AmB and their impact on the ranking of strategies according to their cost-effectiveness, keeping all other variables at their baseline values is shown in figure 3. If MF is purchased at market price ($ 2.68 per capsule), the price per vial of L-AmB would need to decrease to below $12.5 for strategy H to become the most cost-effective strategy. Varying the assumptions regarding indirect cost did not change conclusions.

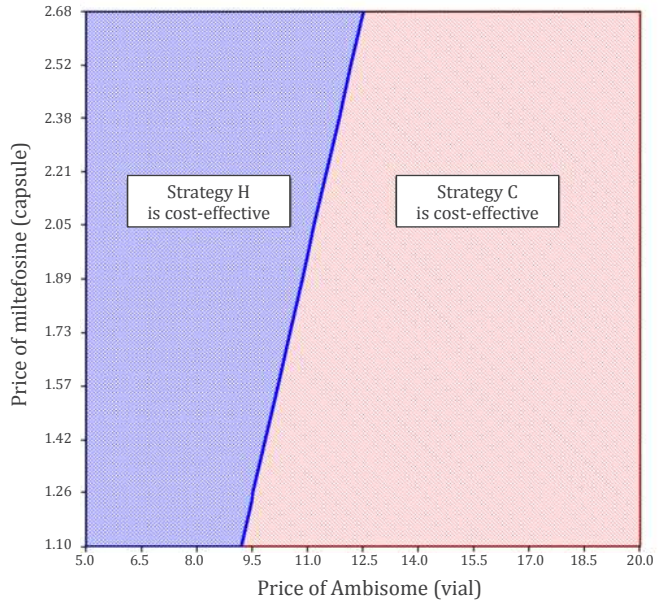

Figure 3: Two-way sensitivity analysis on price of AmBisome and miltefosine.

DISCUSSION

The current first line regimen in the Indian subcontinent is MF for 28 days. There are concerns however that the uncontrolled provision of the drug may increase the likelihood of development of parasite resistance (Sundar & Murray 2005). Even when monitored, patient compliance is not optimal Bhattacharya *et al.* 2007; Sundar & Murray 2005) and the risk remains that women in childbearing age receiving MF do not (or only partially) take contraceptives. Our analysis shows that combination therapies for the treatment of VL are a cost-effective alternative to the current strategy in the Indian subcontinent; this finding may be of interest to control programmes regarding the cost-effectiveness of the currently recommended option. The co-administration of MF with PM for 10 days seems to be the most cost-effective option because of the combined effect of low cost, especially drug cost, and high effectiveness. Also, one would expect that the parenteral intramuscular injection of PM by health workers ensures that patients also take the oral MF as it would be directly observed. With the short treatment duration this is likely to result in high patient compliance, increasing the overall effectiveness of the strategy. Although strategies with L-AmB were the most effective, the high drug cost results in a higher average cost-effectiveness. The next best alternative compared

to the combination MF/PM was a combination of L-AmB with PM with an incremental cost-effectiveness of $652 per death averted. All other strategies, with the exception of a single dose of 10mg per kg of liposomal amphotericine B were dominated. The relatively poor effectiveness for MF monotherapy in our model is linked to the estimated low adherence when using self-administration with 1-weekly drug supplies. However, alternative drug delivery strategies for MF monotherapy are possible. A strategy where intake of MF would be directly observed would result in significantly higher effectiveness, although at higher direct and indirect costs. When we ran a sensitivity analysis with MF compliance put at 100%, this did not change the ranking of strategies or conclusions.

This study is the most comprehensive cost-effectiveness analysis of alternative strategies for the treatment of VL for the Indian subcontinent to date. We used a simple decision analytical model to compare from a societal perspective the cost and outcome of all possible treatment strategies identified through consultation with experts (Delphi method). The demographic probabilities used in the model, as well as the calculation of the average drug cost was based on real patient data on sex, age and weight obtained from a charitable medical facility in India (Olliaro and Sundar 2009), instead of calculating the drug cost of an "average" 35kg patient as done in other studies. In addition, all cost data in the baseline analysis were based on primary data collected from various sites in Nepal and India. Extensive sensitivity analysis was also done to evaluate the robustness of our estimations and conclusions. The analysis has several limitations. *First* while the use of the anthropometric data can be a strength, the VL treatment centre in Muzaffarpur (Bihar) might not be entirely representative for all VL cases, especially with regard to the male to female ratio. Reassuringly, in a larger series of 4170 patients from two locations in Bihar and 1311 from Nepal the male to female ratio was similar (57:43, Olliaro et al, manuscript submitted). Although various studies have reported a higher proportion of male patients to be affected by kala-azar (Singh *et al.* 2006; Thakur 2000) there may be under-reporting of kala-azar in women (Bora 1999) due to sex-selective treatment seeking whereby "fewer women may seek treatment because of its expense" (Thakur 2000). A M/F ratio in the VL population closer to unity could lower the effectiveness of strategies including MF. *Second*, the drug efficacy estimates for the combination treatments, and the monotherapies with L-AmB were based on input from a Delphi survey of VL experts. The uncertainty surrounding these subjective estimates was minimized by including experts that were clinicians and/or involved in clinical trials of combination treatments and dose-finding studies. The uncertainty was also analysed extensively in sensitivity analysis. *Third* the effectiveness estimates are heavily influenced by the parameters of patient compliance to treatment. Experts assumed treatments with parenteral or intramuscular administration to lead to high compliance and oral treatment to result in lower patient compliance. Given the evidence from the international

literature for other diseases, and the limited information available for kala-azar (Bhattacharya *et al.* 2007; Sundar *et al.* 2009), these assumptions seem plausible. As more evidence becomes available from clinical trials (especially Phase IV and other operational studies) and future studies assessing patient compliance, we will update the input parameters and ranges from our model. *Finally*, some cost variables were not included in the analysis. L-AmB requires a cold chain. Because it was difficult to quantify the cost of the cold chain, we did not include it in our calculations and the cost per patient treated and cost per death averted may therefore be an underestimation. There is, moreover, also a substantial risk of breakdowns in the cold chain system, which may impact on the efficacy of the drug. Governments may want to adapt the drug policy choice to the technology constraints in each level of the health system.

Few other studies have investigated the cost-effectiveness of VL treatment strategies. Vanlerberghe et al (2007) (Vanlerberghe *et al.* 2007) compared various monotherapies from a health service perspective (not including paromomycin) and found a strategy with miltefosine to be the most cost-effective with US$328 per death averted. Although the study uses a similar decision tree model and sensitivity analysis to account for uncertainty in the input parameters, the results from this study cannot be compared with ours. The model by Vanlerberghe *et al.* starts with a clinical suspect going through diagnosis and then treatment. Treatment effectiveness is therefore defined by probabilities other than those directly related to treatment such as the prior probability of disease, and the sensitivity and specificity of the diagnostic test. Patient compliance was not modelled either. A more recent study by Olliaro *et al.* (2009) (Olliaro *et al.* 2009) compared various monotherapies and a combination of L-AmB with MF with different total dosages for MF from a health systems perspective. Similar to our findings, Olliaro et al show that the combination L-AmB+MF (for 8 days) with a cost of $124–160 per death averted is more cost-effective than most monotherapies (the exception being PM delivered in an outpatient setting and a 5mg/kg single dose formulation of L-AmB). However this study did not include indirect costs (i.e. productivity losses) underestimating the effect of strategies with a short treatment duration that are beneficial to the patient and household.

Our results highlight that several possible therapeutic options may exist for the South Asian context - especially in light of the ongoing VL elimination campaign in the Indian subcontinent - but combination regimens are efficient options compared to monotherapy. The analysis should be repeated in other VL-endemic areas such as East Africa and Brazil where efficacy outcomes, treatment regimens, direct and indirect costs may differ considerably. Critical elements of importance to national and international policy makers are the cost of drugs, the level of out-of-pocket expenditures by VL patients and compliance to treatment. An obstacle to the introduction of strategies with L-AmB in national control programmes is the cost of the drug.

Despite substantial reductions in the price of AmBisome over the past years (more recently to $18 for a 50mg vial), the threshold analysis showed this to be not enough to make strategies with L-AmB a cost-effective alternative. In addition, the capacity of VL patients and their family to cover the costs of treatment is very limited. VL is a disease that affects the poorest of the poor Boelaert *et al.* 2009 and places a considerable economic burden on households (Meheus *et al.* 2006; Rijal *et al.* 2006; Sharma *et al.* 2006). Especially in India and Bangladesh, the combination of frequent drug shortages and poor quality of care in public health facilities pushes many patients to buy drugs from private pharmacies or to seek care in the private sector. Unless the government or a donation programme covers the cost of drugs, strategies including expensive drugs such as L-AmB will be a barrier to patients and reduce access to appropriate and effective care resulting in increased mortality.

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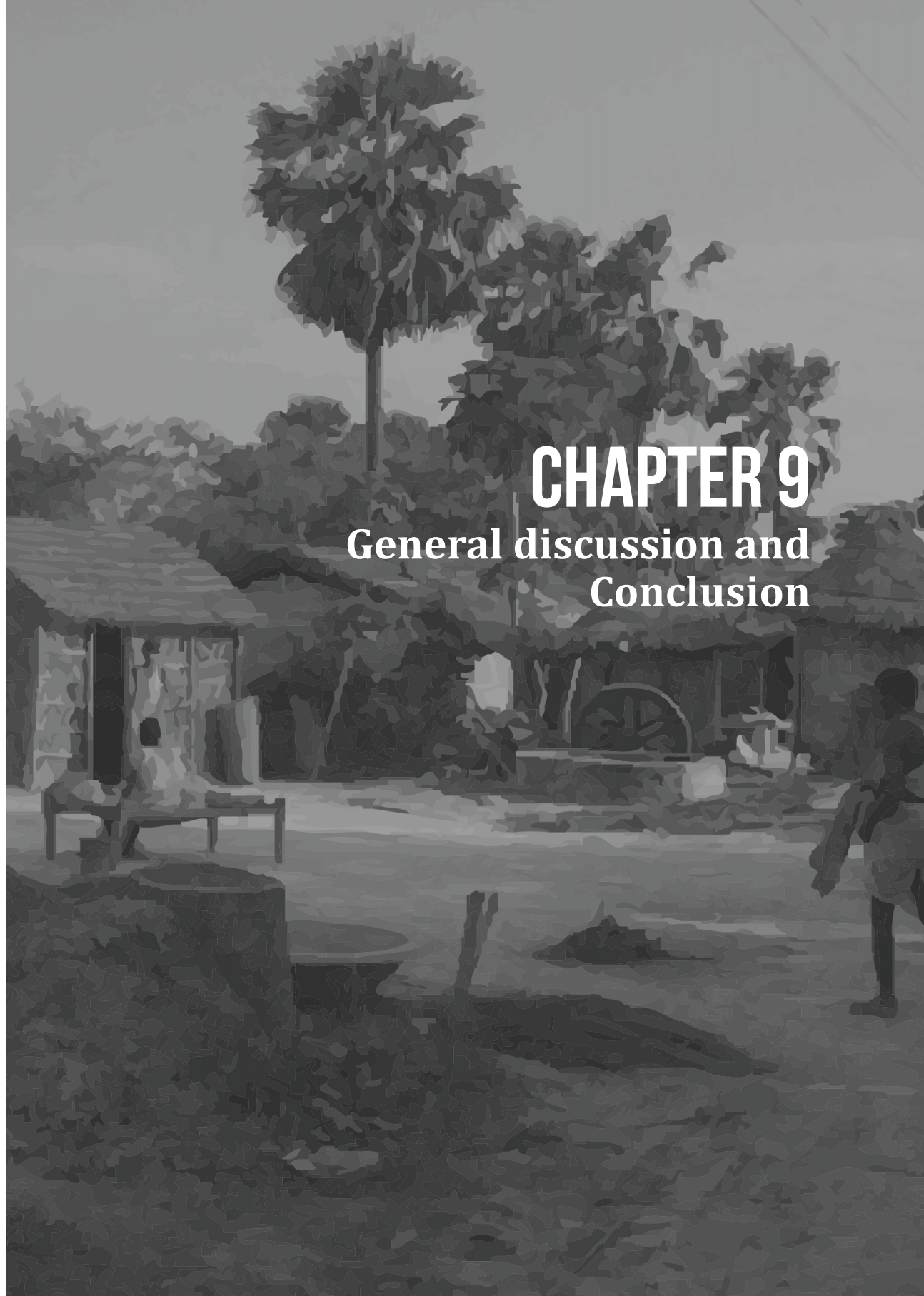

CHAPTER 9

General discussion and Conclusion

The general objective of the thesis was to improve our understanding of the economic aspects of visceral leishmaniasis and to provide evidence for more rational decision making on diagnosis, case management and VL control in the Indian subcontinent and East Africa. To meet this objective, we developed four research questions: (i) What is the burden of visceral leishmaniasis? (ii) What is the health seeking behaviour and costs of VL from the household and provider perspective? (iii) What is the cost and cost-effectiveness of VL treatment strategies? and (iv) What are the policy recommendations that can be formulated on the basis of our findings?

In the following sections I will discuss the findings from the studies presented in this thesis in conjunction with the evolving scientific literature along these research questions, and discuss ongoing research and provide recommendations for future work.

THE BURDEN OF VISCERAL LEISHMANIASIS

One objective of the thesis was to improve our understanding about the burden of VL. The burden of VL can be thought of in terms of the morbidity, mortality and disability as well as the economic and social impact of the disease. In 2010 we published a scientific supplement on the burden of VL in South Asia (Meheus *et al.* 2010) in support of the VL elimination initiative in Nepal, India and Bangladesh with a collection of studies investigating the epidemiological and economic impact of the disease. To build further on the information that was provided in these studies, we highlighted the need for more reliable and in particular routinely collected data on VL incidence and mortality. Recently, Alvar *et al.* 2012 provided updated figures and estimated that between 20 and 40 thousand people die from VL each year. This makes VL one of the most severe NTDs with the highest mortality after schistosomiasis and hookworm infection (Hotez *et al.* 2006). However, unlike the other NTDs, the case fatality rate for untreated VL is 100% and death may occur within a matter of months if the affected individual is left untreated.

The disease burden is now often expressed in terms of disability adjusted life years (DALYs), an indicator that combines (premature) mortality, morbidity and disability in a single metric (Murray and Lopez 1994; WHO 1996). DALYs have become a key measure in the WHO Global Burden of Disease project to determine the disease burden of a wide range of health conditions and are frequently employed by international donors in priority setting and resource allocation. Leishmaniasis is estimated to cause the loss of about 2.1 million DALYs annually (WHO 2004; Mathers *et al.* 2007). However the use of DALYs in priority setting for neglected tropical diseases (NTDs), including leishmaniasis, has been heavily criticized (Lutumba *et al.* 2007; Bern *et al.* 2008; King & Bertino 2008; Reithinger 2008) and estimates are generally

considered too low (Engels & Savioli 2006). Besides the problems discussed in the introduction of the thesis of not having accurate data on mortality and morbidity that are needed for the DALY calculation, DALYs do not take account of the spatial clustering of VL. While at the global, national or sub-national level the burden of VL in terms of incidence, mortality and DALYs may be low, the burden at the community level can be very high. Due to the focal distribution of VL, incidence rates (and underreporting) vary greatly between countries (Mondal *et al.* 2009) as well as between districts and within districts as shown by Das *et al.* (2010). Moreover, VL cases tend to cluster within certain sections of the village at hamlet level and further at household level (Ahluwalia *et al.* 2003; Hasker *et al.* 2012). Incidence rates can be ten times greater at hamlet level (in the range of 1-2% per year) than the aggregate figures recorded at district level (in the range of 1-2 per 1000 per year). Because of the inadequate representation of the burden of disease of VL in terms of DALYs and since VL treatment is a life-saving intervention, we have chosen deaths averted as the unit of outcome to compare treatment alternatives in chapter 8. However, because DALYs are increasingly used in priority setting for health, a re-estimation of the DALYs for VL is necessary as has been done for other NTDs (Luz *et al.* 2009).

In chapter 3 we studied the socio-economic profile of households living in areas with high VL endemicity relative to the general population of Bihar, using data collected from a community intervention trial (i.e. the KALANET trial) and the third Indian National Family Health Survey (NFHS-3). With 83% of households in VL endemic areas belonging to the poorest two quintiles in Bihar, we showed that in areas where VL occurs, the socio-economic status of households is considerably lower than the rest of Bihar. Bihar, in turn, is also one of the poorest states in India. The study confirmed the general notion that leishmaniasis is strongly associated with poverty and affects the “poorest of the poor”. Numerous studies have shown that poverty increases the risk of VL infection or disease, mainly through poor living conditions (Bern *et al.* 2000; Ranjan *et al.* 2005; Schenkel *et al.* 2006; Saha *et al.* 2008; Bern *et al.* 2010; Singh *et al.* 2010a; Hasker *et al.* 2012; Pascual Martinez *et al.* 2012). Killick-Kenrick coined the term ‘paradise for sandflies’ to describe the housing conditions in endemic villages. Damp earthen floors, mud-plastered walls with cracks, proximity to water bodies, soil littered with organic matter, sleeping on the ground etc. are all linked to poverty as well as to increased exposure to peri-domestic sandflies. VL also seems to occur more frequently among scheduled castes in India (e.g. the Mushar caste in Bihar) (Singh *et al.* 2000; Sharma *et al.* 2004; Shah 2005; Hasker *et al.* 2010; Pascual Martinez *et al.* 2012), even after controlling for socio-economic status (Hasker *et al.* 2012). The Indian government rural housing scheme, Indira Awaas Yojana, that provides incentives to people living below the poverty line to construct permanent housing, may help in reducing VL incidence (Government of India 2012).

In summary, VL is one of the most severe NTDs with a 100% case fatality rate for untreated VL. The current estimations of the general burden of disease of VL using DALYs are too low; a re-estimation of DALYs for VL is therefore needed. This also includes revising the disability weight attributed to VL. However an important stumbling block to estimate the general burden of disease of VL remains the uncertainty around incidence and mortality data. We have also shown that VL is strongly associated with poverty and affects the "poorest of the poor".

THE HEALTH SEEKING BEHAVIOUR AND COSTS OF VL PATIENT MANAGEMENT

In part II of the thesis we presented three chapters that analysed the economic burden of VL on the household (i.e. household perspective) in India (chapter 4), Nepal (chapter 5) and Sudan (chapter 6). These studies explored issues related to the health care seeking behaviour of households, direct and indirect costs, and mechanisms to cope with the cost of illness (research question #2). Chapters 4 (India) and 6 (Sudan) also present information on the cost of VL case management from the perspective of the health provider. I will first discuss the results from the provider's perspective followed by a discussion on the economic burden of VL from the household perspective. The cost data presented below was converted to 2010 US dollars using the consumer price index of each respective country to facilitate comparisons between studies.

The aim of the analysis from the providers' perspective was to estimate how much it costs to public (and not-for-profit) health facilities to provide VL treatment for one episode of VL. The evidence on the cost of VL patient management from the perspective of the health care provider is very limited. Only two studies have been conducted so far and were presented in this thesis in chapters 4 and 6 for India and Sudan respectively. Besides informing policy makers about the cost per case treated, the information provided by these studies has been used in economic evaluation studies to compare treatment alternatives for VL (see chapter 8), assess the value of a hypothetical VL vaccine (Lee *et al.* 2012) and can be used to estimate the resource requirements needed for VL control, as is commonly done for other infectious diseases such as HIV/AIDS (Vassall & Compernolle 2006).

In our studies we estimated the medical cost of VL care (drugs, diagnosis, medical supplies, laboratory investigations) and the cost of hospitalization separately by combining step-down cost accounting with an ingredients approach (i.e. bottom-up microcosting). These methods, described in detail in chapter 6, are frequently employed in countries where health information systems and health facility financial records are weak. The estimation in chapter 4 was relatively straightforward since the study was conducted at a non-governmental hospital

in Muzaffarpur in Bihar that provides care for VL only. All costs made by the hospital could therefore be directly allocated to VL patient management. In Sudan (chapter 6) estimations were more complex as VL care represented only a small proportion of overall activities in two out of the three hospitals that were included in the study. Despite the methodological challenges, we believe the cost data to be accurate since most of the data related to the medical costs of VL care were collected using microcosting whereby the actual resource consumption by patients was examined. Although time consuming, microcosting is generally considered to provide the most precise estimates of the costs of care (Drummond *et al.* 2005).

The study in India was conducted at a time when amphotericin B was provided at not-for-profit hospitals, while sodium stibogluconate (SSG) was still the first line treatment at public health facilities, despite the reports about unresponsiveness to the drug in the Indian subcontinent (Sundar *et al.* 2000; Rijal *et al.* 2003). In India, non-governmental health facilities, alongside the private sector, are common sources of treatment for VL patients (Mondal *et al.* 2009; Sundar *et al.* 2010). Although a different first line drug is now used, the daily cost of hospitalization, or unit cost per inpatient day, is likely to remain about the same since medical costs were excluded in its calculation. Our definition of unit cost was also similar to the WHO definition of a "hotel" unit cost (WHO-Choice 2012) and would now be equal to 4.6 US dollars in 2010 values. Obviously, the longer the treatment duration, the higher the cost of hospitalization will be (i.e. duration of treatment multiplied by the unit cost per inpatient day). The cost of hospitalization represented a third of the cost of VL patient management, with drugs and laboratory investigations (i.e. medical costs) each representing a third as well (VL drugs accounted for 71% of the drug costs). These medical costs were very specific to the type of VL drug used. With amphotericin B, patients were regularly submitted to laboratory investigations to test for toxicity and side-effects related to the drug, leading to a high cost for the hospital. Since not only the type of VL drug used but also the prices of these drugs may change over time, regular updates of the cost estimations are needed.

In Sudan, the cost of hospitalization was the largest cost driver in the hospitals included in the study with nearly 80% of the total cost of VL patient management. This was caused by the fact that patients were hospitalized for 30 days of treatment with SSG. The remaining 20% of the cost of VL patient management consisted mainly of the cost of SSG; few laboratory investigations were done. While the average unit cost per inpatient day across health facilities was 5.7 US dollars, we observed a large variation between facilities. Unit cost estimates are particularly sensitive to (inaccurate) activity data and there were some concerns regarding the activity statistics of the hospitals. Only crude information was available on patient throughput needed to calculate the cost per inpatient day. Although information on the number of admissions was

available, statistics on the length of stay by disease category was not centrally available and had to be derived from a sample of medical records.

In terms of the economic burden of VL to households (i.e. household perspective), the following conceptual framework can be derived from our studies:

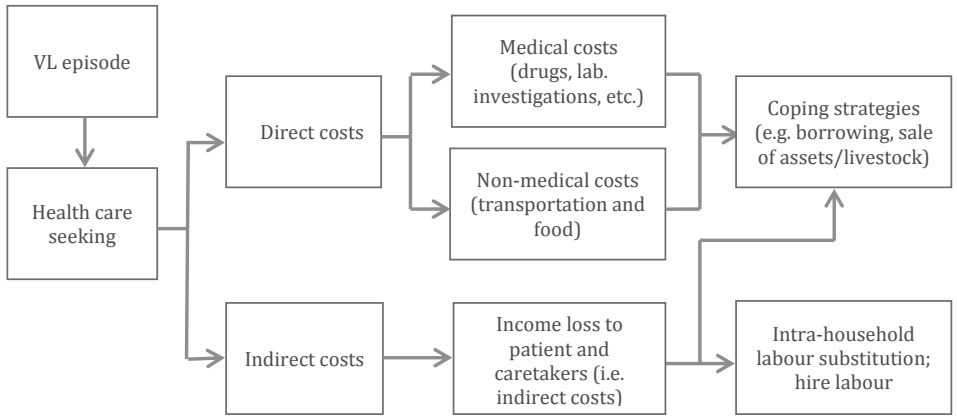

Figure 9.1: Conceptual framework on the economic burden of VL to households

Our studies find that patients usually presented to a qualified health provider with a delay of one to two months. The type of provider first visited varied between countries. This was not unexpected given the important differences in the organization of the health care system between countries.

In India, where the private sector plays an important role in the provision of health care, our findings showed that patients most often visited either a private qualified or unqualified provider first; less than a third of patients that visited a private qualified provider were diagnosed with VL on their first visit. Several studies published in recent years confirmed our findings and showed that the health seeking behaviour of patients had not changed (Sundar *et al.* 2010; Sarnoff *et al.* 2010; Hasker *et al.* 2010) and private providers continued to be an important primary source of care for affected households.

In Nepal and Sudan the majority of patients had first consulted a public provider. In Nepal, our study showed some differences with previous studies conducted in the country that had shown that traditional providers were most commonly the patient's first choice of provider (Sharma *et al.* 2004; Adhikari and Maskay 2005). These studies were carried out nearly a decade ago; a knowledge attitudes and practices survey carried out in 2006/07 had shown knowledge of

VL to be reasonable in VL endemic areas in Nepal with patients mainly using the public sector, similar to our study (Mondal *et al.* 2009). In addition, the presence of the BP Koirala Institute of Health Sciences (BPKIHS) in our study area may have influenced the health seeking behaviour of households and referral practices of health providers. The BPKIHS is a tertiary level hospital situated in Sunsari district that has a widespread reputation in surrounding areas as a VL treatment and research centre.

In the case of Sudan there are not many qualified private practitioners in rural areas (WHO-EMRO 2006) and nearly all patients had visited a public provider, either a village health worker, primary health care centre or public hospital. We found that few patients in Sudan were diagnosed with VL on their first visit, also among those visiting a public hospital. While Gerstl *et al.* (2006) had shown that VL knowledge was limited among community health workers, our data seems to indicate that with the exception of VL dedicated treatment centres, the knowledge of VL is also low at public hospitals and primary health care centres. However our findings on health seeking behaviour in Sudan need to be interpreted with caution because investigating health seeking behaviour was not the primary objective of the study and only quantitative data was collected. Despite this limitation, it is clear that more training is needed among health workers at all levels in highly endemic areas to strengthen the early diagnosis of VL, especially since diagnosis and treatment of VL is the only control strategy currently implemented in Sudan.

At the time of the review presented in chapter 2, there had been seven studies that estimated the financial and/or economic costs of VL in India (Meheus *et al.* 2006 (chapter 4); Sarnoff *et al.* 2010; Sundar *et al.* 2010), Nepal (Sharma *et al.* 2004; Rijal *et al.* 2006; Adhikari *et al.* 2009) and Bangladesh (Sharma *et al.* 2006). There had been no published studies on the economic impact of VL in East Africa. Since then, two additional studies have been published (presented in this thesis), including one study for Sudan (chapter 6). So far, all studies estimated the economic impact of VL at the micro-economic level, i.e. at the level of the household. No studies have assessed the economic impact of VL at the macroeconomic level. Although the severity of disease is high it is unlikely that VL will have an impact on for example gross domestic product as has been shown for malaria or HIV/AIDS (Gallup & Sachs 2001; Dixon *et al.* 2002; Jefferis *et al.* 2008). The majority of VL affected patients are not economically active as primarily young people are affected, and those that are working are mainly employed in the informal sector or subsistence agriculture.

From the perspective of the household, there are two types of costs that can be associated with an episode of VL. Direct costs are (out-of-pocket) expenses incurred by households when seeking treatment. These costs can be broken down into medical (e.g. diagnosis, drugs or

laboratory investigations) or non-medical costs (e.g. food, transportation). Indirect costs were defined as the lost economic productivity due to VL illness to the patient and family members taking care of the patient. We used a uniform definition of costs across the three studies included in this thesis to ensure comparability, which was sometimes an issue with the studies identified in chapter 2.

The studies presented in section 2 (chapters 4-6) of the thesis showed that the economic burden of VL illness is considerable and in most cases catastrophic. We found that indirect costs were larger than direct costs in Nepal and India, while direct costs greatly exceeded indirect costs in Sudan. The duration of illness and the length of treatment were important determinants of costs in all three studies.

In terms of the direct costs, the proportions spent by households on medical and non-medical services varied by type of VL drug used and the patient management process in each country. Expenditure on VL drugs were the largest in India (chapter 4). While most medical services were provided free of charge to patients, VL drugs (at the time amphotericin B) had to be retrieved by the patient or a family member outside the hospital at a local private pharmacy and brought back to the hospital where they were administered intravenously by the medical personnel. In Nepal and Sudan, VL diagnosis and drugs were provided free of charge to patients at public health facilities. Similarly to Nepal, miltefosine is now increasingly being used in India (Banjara *et al.* 2012) as recommended by the VL elimination initiative and both NGO clinics and public health care facilities provide VL drugs and diagnostics for free. The provision of free VL drugs should reduce the economic burden of VL to households. Although two additional studies were published for India in 2010 (i.e. Sundar *et al.* 2010; Sarnoff *et al.* 2010), the data for these studies was collected only two years after our study, prior to the actual implementation of the VL elimination initiative and households still had to pay for the VL drugs in these studies.

In Nepal (chapter 5), the data for the study was collected in 2011 and we examined whether the VL control efforts by the government resulted in a decrease in household costs. The study was not experimental (e.g. pre-post test design) but descriptive and data was collected from patients that were treated for VL at public health care facilities and identified from the medical records of the District Public Health Office (DPHO) of 5 districts and the BPKIHS. We found that overall the costs of a VL episode were one third less compared to the studies carried out prior to the VL elimination initiative. Despite the free provision of VL drugs, we found that the direct costs of an episode of VL were still high due to out-of-pocket expenditures on ancillary drugs, in particular for households that had visited a private provider prior to receiving VL treatment, as well as food costs during treatment.

In Sudan (chapter 6), SSG was provided as first line treatment where it is still efficacious. Because VL drugs are provided free of charge, direct medical costs were small compared to non-medical costs. The largest cost component to households were food costs for the patient and caretakers when hospitalized for VL treatment. Patients are hospitalized for the full duration of treatment of 30 days to ensure 100% adherence and to monitor for adverse events. Due to severe anaemia and malnutrition patients are at high risk of complications and death (Collin *et al.* 2004). Because patients are always accompanied by one or more family members for the entire duration of hospitalization, food costs represent 78% of the median direct cost. These high food costs were also observed in India and Nepal, and are not often taken into account but are an important determinant of the financial burden of VL to households. Since the food costs are caused by the long hospitalization of the patient, alternative treatment regimens with shorter treatment durations will have a considerable impact on the total cost of a VL episode.

Indirect costs were measured according to the human capital method whereby we quantified the loss of productivity in terms of foregone earnings to the patient or other household members taking care of the patient; unpaid household work was excluded. Basically the median number of days of inactivity due to VL illness was multiplied by the median daily income of the individual (either the patient or another household member). We also considered intra-household labour substitution which is a common strategy that households use to mitigate income losses.

Our studies showed that in India and Nepal, indirect costs represented a considerable proportion of total costs (58% and 53% respectively). VL is characterized by prolonged fever, weight loss, anaemia, fatigue and enlargement of the liver and spleen. As a result patients are either severely limited or not able at all to carry out their daily activities and need much support from family members. We found that patients were not able to work for a median number of 51, 57 and 70 days in Sudan, Nepal and India respectively. The long inactivity of patients was caused by a combination of the delay between the onset of symptoms and the time the patient is correctly diagnosed for VL and the long duration of treatment. Most of the economically active patients in India and Nepal were working as daily labourers such as rickshaw driver or farm labourer. When falling ill, they were rarely replaced by other household members. In contrast indirect costs in Sudan represented only 14% of the total cost of a VL episode. Subsistence farming was the main activity of households in Sudan and there were less patients and caretakers economically active in Sudan compared to India and Nepal. However, in households with a working patient reporting income losses due to VL illness, indirect costs represented 40% of the total cost of a VL episode.

In table 9.1 we summarized direct and total costs (direct and indirect) as a proportion of annual household income by all studies that were carried out in the Indian subcontinent and East Africa. Given the variation in methods between studies, both in terms of the classification of costs and summary statistics used (e.g. median vs. mean values), comparing these results across countries need to be done with caution.

With the exception of two studies in Nepal (including our study presented in chapter 5), household expenditure on medical and non-medical items (i.e. direct costs) were catastrophic to households. Combined with the income losses due to VL illness, the burden of an episode of VL was very high in all studies. We determined costs as catastrophic if they exceeded 10% of annual household income (Ranson 2002). It is hypothesized that if costs incurred by households exceed this threshold, they will need to cut expenditure on basic goods and services, incur debt or sell productive assets which may lead to impoverishment. This is obviously a somewhat arbitrary cut-off point; as we have seen in chapter 3, VL affected households are very poor and have therefore a limited ability to cope with the costs of illness. The catastrophic threshold for these households may therefore be well below this cut-off point.

Table 9.1: Overview of studies investigating the economic burden of visceral leishmaniasis in the Indian subcontinent and East Africa

Authors	Country	Sample size (HHs)	Direct costs as % of annual HH income[2]	Total costs as % of annual HH income[2,3]
(Ch. 4) Meheus *et al.* 2006	India	77	14.8	21.7
Sarnoff *et al.* 2010	India	182	11.3	16.0
Sundar *et al.* 2010	India	171	27.8	na
Adhkari & Maskay 2003; 2005[1]	Nepal	18	15.5	35.6
Rijal *et al.* 2006	Nepal	20	7.2	17.1
Sharma *et al.* 2004; Adhikari *et al.* 2009[1]	Nepal	61	14.1	36.9
(Ch. 5) Uranw *et al.* 2012	Nepal	168	3.9	11.0
Sharma *et al.* 2006	Bangladesh	87	16.1	23.3
(Ch. 6) Meheus *et al.* 2012	Sudan	75	16.6	23.0

HH = household; na = not available
[1] These studies used the same dataset of households
[2] Median values except studies by Adhkari & Maskay 2003; 2005 that presented mean values. These figures are likely to overestimate the median values.
[3] Total costs include direct and indirect costs.

In our studies, total household costs per episode of VL were as much as 23% of annual household income in Sudan and nearly 22% in India. In Nepal the economic burden of VL was lower but still catastrophic at 11% of household income. However, in our studies we analysed costs for the last episode of VL. Because of the clustering of VL in communities and villages, several cases of VL often occur in the same household. For example , 31% and 44% of households in Sudan and Nepal respectively had experienced a case of kala-azar before, often within a few years. More than one episode of VL in the household will significantly increase the burden of VL. Even if these cases do not occur in the same year, the risk of impoverishment and indebtedness would still be much higher.

The economic impact of a VL episode is not limited to direct and indirect costs, but also the strategies used by households to cope with the costs of illness add to the burden of VL. These strategies address direct costs (e.g. using savings or borrowing) and/or indirect costs (intra-household labour substitution) (Sauerborn *et al.* 1996). We observed some differences in the coping strategies employed between the Indian subcontinent (India and Nepal) and Sudan that were related to the capacity of households to raise money to pay for the costs of care. In Nepal and India, the first and most common strategy used by households was the mobilization of savings or use of available cash. These "savings" or cash were usually intended to buy food. For the majority of households this was not sufficient to cover the costs of care and 56% and 81% of households in Nepal and India respectively had also to take a loan. The terms of the loan varied depending on the source of the loan (e.g. from friends/family or a money lender). For instance in Nepal, households had to repay on average 140% of the original amount borrowed when borrowing from either an informal money lender or a village member. In contrast in Sudan, few households had savings and relied on cash gifts from village members (59%) or sold crops (57%) or livestock (38%) to raise money. The timing of the survey in Sudan may have influenced the coping strategies as the survey was taken after the harvesting period. About 5% of households in Sudan sold part of their land to pay for the costs of care. Strategies to cope with the indirect costs of illness included intra-household labour substitution and hiring labour to replace the ill household member. In 24% of households in Nepal, children were involved in preserving the income of the household and were removed from school for the duration of illness to replace the VL patient.

In summary, the free provision of VL diagnosis and drugs has been an important policy measure in reducing financial barriers and improving access to VL care. Without this policy the economic burden of VL would have been much higher. However, given the extreme poverty of VL affected households, a VL episode is still catastrophic to most households. One of the main cost determinants to both public hospitals providing VL treatment and households is

the duration of treatment and length of hospitalization. In addition households also incur substantial costs during the health seeking phase (prior to correct VL diagnosis) as well as through the strategies they use to cope with the cost of illness such as loans.

THE COST AND COST-EFFECTIVENESS OF VL TREATMENT STRATEGIES

Part III of the thesis included two studies and investigated the third research question: "*What is the cost and cost-effectiveness of VL treatment strategies?*". In this section, I will also place the cost and cost-effectiveness findings within a context of priority setting for VL research and control.

Early diagnosis and effective treatment is the main control strategy for VL; in East Africa it is the only strategy that is currently available. Against the background of limited treatment options for VL, and the importance of preserving existing drugs against the development of resistance (see introductory chapter), we reviewed in chapter 7 the evidence and explored the potential of combination therapy for the treatment of VL. With no new compounds expected to come to the market in the near future and the risk of resistance to new medicines, combination therapy is brought forward as a possible alternative. Combining drugs from different chemical classes could also reduce treatment duration or total drug doses, resulting in fewer toxic effects, higher compliance, and less burden on the health system. Combination therapies may also reduce the overall costs (direct and indirect) and be more cost-effective which we will discuss in the next paragraphs.

In chapter 8 we assessed the cost-effectiveness of all possible mono- and combination therapies for the treatment of visceral leishmaniasis in the Indian subcontinent using a decision analytical model based on a decision tree. The analysis was done from a societal perspective and included all costs irrespective of whether they were borne by the government or the patient/household (i.e. health provider and household perspective). We included the household perspective in the analysis since treatments with shorter duration may result in important cost savings to the household. The values related to drug efficacy for therapies that were still in clinical trials at the time of the study were derived through an iterative consultation procedure with a group of VL experts (i.e. Delphi process). These experts were clinicians and/or involved in clinical trials of combination treatment and dose-finding studies. The estimates provided by VL experts proved to be very accurate and were confirmed recently by a phase 3 trial published in 2011. In this study Sundar *et al.* (2011) reported definitive cure rates of at least 97% for the three combination therapies included in our cost-effectiveness study (i.e. 10 days each of miltefosine and paromomycin (MF+PM), single -dose liposomal amphotericin B and 10-day paromomycin (L-AmB+PM); and single-dose liposomal amphotericin B and 7-day miltefosine (L-AmB+MF)). The treatment durations of these combination therapies were also considerably shorter (range 8-11 days) compared to current monotherapies (range 21-28 days) and corresponded to the values used in our analysis.

Our results suggested that a combination of miltefosine and paromomycin (MF+PM) provided the lowest cost-effectiveness ratio at US$92 per death averted. The next best alternative was L-AmB+PM with an incremental cost-effectiveness ratio of US$ 652. Due to a high drug efficacy and expected compliance, the most effective treatment option was a single dose of 10mg per kg of liposomal amphotericin B (L-AmB10). This treatment is also recommended by WHO as the preferred monotherapy (WHO 2010; Matlashewski *et al.* 2011) as it is safe and effective and only a single dose is needed allowing point-of-care diagnosis and treatment on the same day (Van Griensven & Boelaert 2011). Such a strategy would significantly reduce the economic burden to households and would relieve public health care facilities in VL endemic areas particularly during the peak transmission periods. However, L-AmB needs to be administered intravenously and stored below 25°C. In addition, the incremental cost-effectiveness ratio of L-AmB was US$ 8,224 due to the cost of the drug which is its main barrier to widespread use. Although price negotiations between the WHO and the manufacturer reduced the price of L-AmB to US$ 20 per vial at the time of the study, as several vials are needed per treatment course the total cost of L-AmB was higher than any of the combination therapies. For L-AmB to become the most cost-effective strategy, we showed in our study that the price would need to be reduced to under US$ 10 per vial. Since our study, the price of L-AmB has further decreased to US$ 18 per vial, which will lower the cost of L-AmB strategies but will not change the conclusions of our study.

What are the implications of our findings from the Indian subcontinent to East Africa? The results from chapter 8 cannot be extrapolated to East Africa because of the geographical heterogeneity of VL (van Griensven & Boelaert 2011) and differences in the cost structure between countries (Hutton & Baltussen 2005). For example a phase III study in Africa showed that the cure rate of 15 mg/kg per day of paromomycin for 21 days was inadequate, in particular in Sudan (Hailu *et al.* 2010). Several other clinical trials evaluating combination therapies are currently underway in East Africa (Omollo *et al.* 2011). Similar to the study that was done in the Indian subcontinent, we are currently evaluating the cost-effectiveness of various treatment regimens for Sudan and pending the results from the clinical trials I present here some findings on the costs of the various VL treatment strategies that are currently being evaluated in Sudan. These include 3 combination therapies (strategies 1-3) and 4 monotherapies (strategies 4-7) (table 9.2).

Table 9.2: Overview of possible treatment strategies in Sudan

	Strategies	Length of treatment (days)
1	L-AmB (10MK) + MF (50/100 MD)	11
2	L-AmB (10MK) + SSG (20 MKD)	11
3	SSG (20 MKD) + PM (15 MKD)	17
4	L-AmB (30 MKD)	10
5	SSG (20 MKD)	30
6	MF (50/100 MD)	28
7	Glucantime (20 MKD)	20

L-AmB : Liposomal Amphotericin B; MF : miltefosine; SSG: Sodium stibogluconate; PM : paromomycin
MK = mg/kg single dose; MD = mg per day; MKD = mg/kg body weight per day.
Miltefosine if given at 50 mg/day if body weight is <25 or 100 mg/day if body weight ≥ 25 kg.

The costs of the various treatment alternatives are as follows (table 9.3):

Table 9.3: Cost estimates of each treatment strategy per patient treated (US$ 2010)

	Strategies	Drug cost	Other direct medical[1]	Non-medical & indirect	Total cost[2]
1	L-AmB + MF	139.6	64.9	41.1	245.6
2	L-AmB + SSG	148.0	64.3	41.1	253.4
3	SSG + PM	41.5	99.1	63.5	204.0
4	L-AmB	378.0	64.1	37.3	479.5
5	SSG	51.3	173.5	112.0	336.9
6	MF	38.1	163.5	104.5	306.1
7	Glucantime	42.0	115.7	74.7	232.4

[1] Calculated using the average hotel unit cost of US$ 5.74 across the three hospitals
[2] The cost estimations are preliminary as more definite information on resource usage may become available from the clinical trials.

The category "non-medical and indirect" costs are entirely borne by the households while the other two categories ("drug" and "other direct medical") are mainly borne by the health care provider. With the exception of treatment with L-AmB, all other alternatives are cheaper than the current first-line treatment SSG. While a MF-strategy has the lowest drug cost, these are largely offset by the high cost of hospitalization and the household costs. As explained in chapter 6, VL patients in Sudan are hospitalized for the entire duration of treatment. This is also likely to be the case with the oral drug miltefosine. In contrast the shorter treatment durations

and resulting low cost of hospitalization and household costs of combination therapies with a low dosage of L-AmB (requiring fewer vials than the monotherapy) "compensates" for the higher cost of the drug. The cheapest strategy was a combination of SSG and PM at US$ 204.

Priority setting for neglected tropical diseases (NTDs) – making a case for investment in visceral leishmaniasis control

In the past decade, a renewed interest in NTD research and control has emerged in both the public and private sectors leading to the establishment of various initiatives and public-private partnerships (PPPs), such as the World Health Organization NTD programme, the USAID programme on NTDs, the Global Network for NTDs (GNNTD), the Drugs for Neglected Diseases Initiative (DNDi) and various vertical initiatives such as the Schistosomiasis Control Initiative (SCI). An important milestone was reached end January 2012 in London where global health leaders, national and international policy makers and the heads of major pharmaceutical companies committed to control or eliminate 10 neglected tropical diseases (NTDs) by the end of 2020. The London Declaration on Neglected Tropical Diseases endorsed during this meeting followed years of intense advocacy efforts conducted to increase public awareness and funding for the NTDs.

Advocates were particularly successful in raising the profile of seven NTDs described as "tool-ready" by WHO by demonstrating the low cost and cost-effectiveness of interventions to control these diseases. The seven NTDs include six helminthic infections (soil-transmitted helminths (ascariasis, trichuriasis, hookworm), lymphatic filariasis, onchocerciasis and schistosomiasis) and a bacterial infection, trachoma. The main control strategy consists of providing single doses of one or more drugs (albendazole, ivermectin, praziquantel and/or azithromycin) targeting the seven NTDs once or twice per year through mass drug administration (MDA) based on the WHO guidelines for preventive chemotherapy (WHO 2006). Strategies are low-cost (and safe and effective, hence the term "tool-ready) because most of the drugs are donated by private pharmaceutical companies (Fenwick *et al.* 2005) or purchased at low prices. Diseases such as VL or human African trypanosomiasis (HAT) were not considered among these "tool-ready" diseases.

While the emphasis on low-cost and cost-effectiveness were strong arguments to make a case for investment in the "tool-ready" NTDs (Molyneux *et al.* 2005; Canning 2006; Hotez *et al.* 2009; Ruxin 2009; Conteh *et al.* 2010), it was less "beneficial" for other NTDs that currently lack (known) cost-effective interventions and do not receive similar support from private pharmaceutical companies (the "tool-deficient" diseases). VL or HAT therefore risk being labelled low priority by national programmes and international donors.

With the evidence presented in this thesis and elsewhere, can we make a case for investment in VL? How cost-effective is VL treatment and how cost-effective is VL treatment relative to other neglected tropical diseases?

The cost-effectiveness study presented in chapter 8 showed that average cost-effectiveness ratios for VL treatment ranged from US$ 91 to US$ 162 per death averted depending on the type of drug regimen. With a cost less than US$ 100 to save a life (for treatment with MF+PM), this seems to be very good "value for money". There is however no universal threshold value below which an intervention is generally considered cost-effective. Suggested thresholds consider an intervention to be very cost-effective when the cost-effectiveness ratio is lower than gross domestic product (GDP) per capita and cost-effective if it is between 1 and 3 times GDP per capita (Commission on Macroeconomics and Health 2001; WHO 2012). In the case of our study in chapter 8, relative to the country with the lowest GDP in the Indian subcontinent (i.e. Nepal with US$ 620 in 2011; World Bank 2012) VL treatment can be judged a highly cost-effective intervention. Others suggested an intervention to have a "highly attractive" cost-effectiveness if the cost per DALY averted is less than US$ 25 and "attractive" if it is less than US$ 150 (World Bank 1993). As explained in the first section of this discussion, we had chosen deaths averted as an outcome measure since VL treatment is a lifesaving intervention. Because comparative assessments are now often done in terms of disability adjusted life years (DALYs) (e.g. the Disease Control Priorities in Developing Countries project (Jamison *et al.* 2006), I provide here an approximation of DALYs for VL. DALYs are calculated as the sum of the years of life lost due to premature mortality (YLL) and the years of life lived in disability (YLD) (Murray & Lopez 1996; Fox-Rushby & Hanson 2001). DALYs were calculated following the approach by Fox-Rushby & Hanson (2001) using a number of simplifying assumptions[1]. Firstly I assumed a 100% case fatality rate for untreated VL and instantaneous death once clinical symptoms occur although the time period between the onset of symptoms and death for untreated VL is about 3 to 5 months. Secondly, given this brief time period between the onset of symptoms and death for untreated VL, YLDs as a share of total DALYs is likely to be small. Since long-term disability after VL treatment is also infrequent, YLDs were not included in the DALY calculation[2]. The

[1] The formula used to estimate YLLs is as follows (Murray & Lopez 1996; Fox-Rushby & Hanson 2001):

$$YLL[r,K,\beta] = \frac{KCe^{ra}}{(r+\beta)^2}\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1] - e^{-(r+\beta)a}[-(r+\beta)a-1]\} + \frac{1-K}{r}(1-e^{-rL})$$

Where: K = age weighting modulation factor; C = Constant; r = discount rate; a = age of death; = parameter from the age weighting function; and L = standard expectation of life at age a.

[2] There are also some important methodological issues with the estimation of YLDs for VL, in particular related to the disability weight (DW), which is a measure of disease severity. The DW for VL is 0.243 (Mathers *et al.* 2007) and is too low (a score of 0 represents perfect health and 1 equals death). For example, the weight for an uncomplicated episode of malaria is much higher at 0.471, while we found from our surveys that the vast majority of VL patients are not able to engage in productive activities at all when ill.

data on life expectancy at age *a* were derived from life tables for Nepal (Lopez *et al.* 2001) and DALYs were calculated in five-year age intervals using data on age distribution from our household survey in Nepal (chapter 5).

In the absence of VL treatment, the total number of DALYs [0.03,1,0.04] lost per person equals 30.1. This number is relatively high because (i) untreated VL is fatal and (ii) many cases of VL occur among young adults that are given more weight in the DALY estimation. Without age weighting (K=0), the total number of DALYs [0.03,0,0] lost equals 24.6. Carrying out the analysis for the strategies MF+PM, L-AmB+PM and L-AmB (10mg/kg) of chapter 8, we find that cost-effectiveness ratios vary from US$ 2.9 to US$ 5.1 per DALY averted. The only other estimation available in the literature on DALYs for VL was made by Griekspoor *et al.* (1999). They estimated the cost-effectiveness of VL treatment in an emergency situation in Sudan and obtained a cost-effectiveness ratio of US$ 18.4 per DALY averted. This estimate is higher than ours because the average cost per patient treated was higher (i.e. US$ 394) and the authors assumed a case fatality rate for untreated VL below 100%.

Compared to other neglected tropical diseases, our estimates are very similar to those for mass drug administration for lymphatic filariasis (US$ 4 to US$ 8 per DALY averted) (Jamison *et al.* 2006; Laxminarayan *et al.* 2006; Ottesen *et al.* 2008) and combined school-based treatment of intestinal worms and schistosomiasis (US$ 10 to US$23 per DALY averted) (Miguel & Kremer 2004; Conteh *et al.* 2010).

In summary, we have shown here that interventions for VL treatment are within the range of highly cost-effective public health interventions (Laxminarayan *et al.* 2006). A number of observations need to be made regarding this finding. First, as we have seen throughout our studies, both the measurement of the general burden of disease through DALYs and cost-effectiveness estimates (cost per DALY or death averted) "hide" the economic burden of VL to patients and their family. While interventions may be cost-effective, they ignore the substantial hardship that is placed on households. As we have shown in our studies in Nepal and Sudan even in situations whereby patients are not charged for diagnosis or VL drugs, households still incur high costs mainly as a result of the long duration of hospitalization and the delay to correct VL diagnosis. Implementing treatment interventions with shorter treatment duration, such as combination therapies, are therefore a crucial component in reducing the cost to households. A limitation of current studies is that they only captured the short-term effects of VL illness. In the studies presented in section 2 of the thesis, we have mainly documented household direct and indirect costs, as well as the strategies used by these households to cope with these costs. No studies to data have examined the long term effects of a VL episode and

the coping strategies used on the wealth and livelihood of affected households. Better insights into these processes may provide additional arguments for investing in VL treatment and in particular prevention, and find ways to mitigate the economic burden of VL.

Secondly while VL treatment may be very cost-effective according to the thresholds mentioned in previous paragraphs, this does not mean however that VL treatment is affordable to national VL control programmes. The issue of affordability is an often forgotten criterion in health-care priority setting (Cleary and McIntyre 2009). While the cost per death or DALY averted is relatively low, VL occurs in countries facing many competing health priorities and constrained health resources. It is therefore necessary to not only estimate the cost and cost-effectiveness of interventions, but also the budgetary impact of VL control. With the recent updated estimates of VL incidence, such an estimation is now possible although the authors of the study acknowledge that uncertainties inherent in their data remain (Alvar *et al.* 2012). In addition, continued advocacy is needed to bring the price of VL drugs further down, in particular the price of liposomal amphotericin B. End 2011, Gilead Sciences, the manufacturer of AmBisome® (i.e. liposomal Amphotericin B), signed an agreement with WHO to donate drugs that will allow 50,000 patients to be treated in the next 5 years. With 10,000 patients per year, this donation only covers a small proportion of the annual number of VL cases. While drug donations are essential during emergency relief situations, such as a VL epidemic, more sustainable solutions should be promoted such as reducing the price of AmBisome® rather than relying on drug donations. According to a press statement released as part of the London Declaration on NTDs (United to Combat NTDs press release 30/01/20123), "*Gilead, …, will continue its program to offer VL at cost and commit to investigate and invest in technologies and processes that could reduce that cost in resource-limited countries*". The "no-profit" price of AmBisome® is US$ 18 per vial (Gilead press release 20114); as we have shown, the price per vial of AmBisome® needs to be reduced below US$ 10 to become the most cost-effective strategy to treat the disease.

RECOMMENDATIONS FOR VL POLICY

The free provision of VL diagnosis and drugs have been important policy measures to lower financial barriers and improve access to VL diagnosis and care. Without this policy the economic burden of VL would have been much higher. However, the economic impact of VL is still considerable and intensified efforts are needed to further reduce the burden of VL for

[3] United to Combat Neglected Tropical Diseases Press Release, 30 January 2012: http://www.unitingtocombatntds.org/downloads/press/ntd_event_press_release.pdf

[4] Gilead Sciences Press Release, 08 December 2011: http://www.gilead.com/pr_1637695

affected households. The implications of the studies presented in this thesis conducted from various perspectives call for a change in current policies.

On the basis of our findings, the following recommendations can be formulated:

→ Reduce delays between onset of symptoms and correct VL diagnosis.

The costs incurred by patients can basically be divided in two time periods: (i) costs incurred prior to correct VL diagnosis during the health seeking phase and (ii) the costs incurred when receiving treatment (discussed in the next paragraph).

We have shown that households incur substantial expenses when seeking care. The longer the delay between symptoms onset and access to VL care, the higher the household costs are likely to be. We found that the median lag time between symptoms onset and presentation to a qualified provider was 1-2 months; in particular at private providers in India the patient was not often diagnosed with VL on the first visit. There are a number of lessons that can be drawn here. In India, given the importance of the private sector, there is a need to involve private health practitioners in VL control efforts by ensuring compliance to diagnosis and treatment practices as defined in the national guidelines as well as regular reporting of all diagnosed and treated cases to district health authorities. Since our study, a rural outreach programme has been rolled out in 18 states, including Bihar, with the introduction of voluntary community health workers (ASHA) in every village and additional auxiliary nurse midwifes at sub-centres (Ministry of Health and Family Welfare). Similar to malaria control activities at the community level (Sharma and Dutta 2011), ASHAs can play a role in VL control activities. The rK39 rapid diagnostic test (RDT) is easy to perform and can be used by ASHAs in villages and provide an important contribution to the early detection of VL cases with subsequent referral to primary health care centres for treatment. It seems however that ASHAs and other community workers are not yet involved in the diagnosis of VL (Srivastava *et al.* 2009) and according to a study by Hasker *et al.* (2010), only few VL patients had first reported to ASHAs. Additional investigation into the role of community workers is needed, including studies on the current knowledge, attitude and practices of ASHAs and other health workers active at the community level in India as was done for tuberculosis and the DOTS programme (Sagare *et al.* 2012; Malaviya *et al.* 2012). Unlike the Indian subcontinent, VL diagnosis at the community level by village health workers may not be a feasible strategy in Sudan. Not only does the overall lack of human and financial resources allocated to the VL programme hamper the development of decentralized control policies, recent studies showed varying sensitivity between different brands of the rK39 RDT in East Africa with several RDTs inadequate for excluding a VL diagnosis when used alone (WHO 2011; Cunningham *et al.* 2012).

→ Change the first line treatment

An important determinant of household and hospital (i.e. provider) costs is the duration of treatment of current first line regimens; respectively 28 and 30 days in the Indian subcontinent and East Africa. The extended length of stay poses a significant burden to households and hospitals. As shown in this thesis, households incur substantial non-medical costs, in particular on food, and income losses while the length and cost of hospitalization are a heavy burden to the public health care system especially during the peak transmission period.

Although making strong recommendations about the best treatment options is beyond the scope of this thesis, we have shown that, from a societal perspective, more effective and cheaper alternatives are available. Combination therapies and L-AmB monotherapy are possible alternatives for the current first-line treatment with miltefosine in the Indian subcontinent, while a preliminary cost analysis for East Africa presented above suggest that a combination of SSG and PM is the cheapest and has a similar efficacy to the current first line (Musa *et al.* 2012). The latter strategy is already successfully implemented in East Africa by non-governmental organizations (NGO's) such as Médecins sans Frontières; similarly L-AmB based strategies are also used on a small scale by NGO's in India at the primary health care level and have overcome the cold chain constraints.

The findings on cost and cost-effectiveness presented in this thesis support the clinical evidence to integrate these treatment strategies into national guidelines for the management of VL and are also in line with the recommendations of the WHO expert committee on leishmaniasis. This should be done as soon as possible given the demonstrated economic impact of VL illness and treatment costs on household wealth.

→ Bring the price of L-AmB further down

An important bottleneck to the implementation of L-AmB based treatment strategies and the inclusion of the drug in national guidelines in the Indian subcontinent is its price. Since price and performance are often the main criteria in tender processes and with cheaper alternatives available, it is unlikely that governments will adopt L-AmB treatment strategies at the current price per vial (i.e. US$ 18 per vial; about US$ 280 for a full treatment course). It is therefore necessary to bring the price per L-AmB vial further down. We showed in this thesis that the price of a L-AmB vial needs to be reduced to below US$10 to become cost-effective. However obtaining further price reductions from the manufacturer is not going to be evident. A possible solution could be the use of so called "pull" mechanisms whereby a specified level of demand for the drug is ensured and thereby mitigating the unpredictability in market demand to the manufacturer. Establishing a larger and more credible market for the drug may also stimulate generic manufacturers to develop generic L-AmB formulations which may in turn bring the price further down.

An example of such a pull mechanism is the advance market commitment (AMC) whereby a financial commitment is made for future purchases at a pre-agreed price (Batson *et al.* 2006). Currently AMCs have mainly been used to accelerate the introduction of vaccines in developing countries (e.g. the new pneumococcal vaccines). The potential of these kinds of innovative financing mechanisms to improve access to VL drugs in endemic countries should be further investigated.

→ Reduce household non-medical costs

To mitigate the impact of direct costs to households (medical and non-medical), national control programmes ought to consider introducing demand side financing mechanisms. These financing arrangements are more realistic on the short term than health insurance since coverage of the latter is currently very low or mostly non-existent in the three study countries. Furthermore, insurance primarily covers direct medical costs at accredited formal health care practitioners while we have seen in part II of the thesis that non-medical costs on transportation and in particular food are as important or even greater than direct medical costs.

With demand side-financing households receive a subsidy (i.e. public funds) to purchase defined goods and services in order to improve access to these services. Demand side financing mechanisms include for example voucher schemes or conditional cash transfers. These mechanisms have already been used in the study countries as humanitarian cash transfers on nutrition in Sudan or to improve access to child and maternal health services in India. Demand side financing is feasible for VL since public health authorities in Nepal now provide a one-time payment of Rs 1,000 to households that completed VL treatment to cover transportation costs (Adhikari *et al.* 2011) and is implemented through the district public health offices. Given the importance of food costs, authorities in Nepal should consider expanding the programme to include these costs as well. There is however little information available on the programme in terms of coverage or beneficiaries.

CONCLUDING REMARKS

With a renewed interest in neglected tropical diseases and the implementation of a VL control initiative in the Indian subcontinent, the studies presented in this thesis contributed to ongoing VL policies and research efforts in various ways. With new technologies and treatments that have become available, there was an urgent need to provide national and international policy

makers with sound and systematic economic evidence that enable the design of more rational and effective case management policies. This was particularly important given the resource constraints VL endemic countries face, and the severe economic impact of VL to households.

Equally important was to raise awareness about the economic burden of VL to affected households in order to draw the attention of national and global health policy makers to the need for further action and support in both research and policy. This effort will need to be intensified as VL has received relatively little attention compared to other neglected tropical diseases. Here, economic arguments about cost and cost-effectiveness can contribute to making a compelling case for investment in the control of VL.

Finally, I have studied for my thesis the economic burden of VL and the cost and cost-effectiveness of VL patient management. Improved treatment policies are one side of the story. Successful VL control or elimination will only be possible if sufficient resources are also invested in the prevention of VL through vector control and ensuring access to rapid diagnosis and treatment, removing financial barriers and improving the quality of VL care.

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SUMMARY

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Visceral leishmaniasis (VL) is a vector-borne disease caused by *Leishmania* parasites that are transmitted by the bite of an infected female sandfly. VL is an important public health problem and a significant cause of mortality and morbidity in the Indian subcontinent and East Africa. Since 2005 the governments of India, Nepal and Bangladesh are engaged in a collaborative effort to control and eliminate visceral leishmaniasis from the Indian subcontinent. Approaches to control aim on the one hand at improving the human recovery rate through early diagnosis and case management and on the other hand reducing vector density and biting rate through vector control interventions such as indoor residual spraying (IRS) and the use of bednets. In East Africa such an integrated effort to control VL does not yet exist and control is mainly based on passive case detection and treatment, although bednets are distributed by non-governmental organizations.

VL disproportionally affects the poorest population groups in low-income countries. For the control, or even elimination, of VL to be successful, it will require a great deal of effort that needs to be sustained over the longer term. Ultimately, effective control of VL will depend on a mix of interventions, consisting of early and efficient diagnosis and treatment, with drug regimens that put as little burden as possible on both the patient and the health system. However, the scarcity of reliable data, both epidemiological and economic, contributes to the low visibility and priority given to VL by national disease control programmes and international donors.

Economic analysis provides an important set of tools to underpin the choice for evidence-based policy. Given the limited financial resources available to VL control and the increasing number of possible interventions, especially regarding drug treatment, economic evaluation provides us with methods to systematically compare all relevant options in terms of their costs and consequences and thereby contribute to more rational decision-making and efficient allocation of scarce resources. Moreover it can improve our understanding of factors influencing both the supply of VL interventions and factors related to the behaviour of VL affected households. While economic analysis is increasingly recognized by both national and international policy makers as an important tool in the development of VL control policies, the scarcity of reliable data, in particular on costs, severely hampers efforts to control the disease.

The general objective of this thesis was to improve our understanding on the economic aspects of visceral leishmaniasis, provide evidence for more rational decision making on diagnosis, case management and VL control and justify increased investment in VL research and control in the Indian subcontinent and East Africa.

More specifically, the studies included in this thesis were framed around the following specific objectives: (i) understand the burden of visceral leishmaniasis in India, Nepal and Sudan; (ii) provide a better understanding of the health seeking behaviour and costs of VL illness from the provider and household perspective; and (iii) examine the cost and cost-effectiveness of VL treatment alternatives with a focus on combination therapies.

In terms of the first research question "to understand the burden of visceral leishmaniasis in India, Nepal and Sudan", we provided in ***chapter 2*** an overview of studies that investigated the socio-economic aspects of two neglected tropical diseases: visceral leishmaniasis and sleeping sickness. Both of these diseases affect the poorest of the poor in endemic countries, cause considerable direct and indirect costs (even though the national control programmes tend to provide free care) and push affected households deeper into poverty. In ***chapter 3***, we studied the socio-economic profile of households living in areas with high VL endemicity relative to the general population of Bihar, using data collected from a community intervention trial (i.e. the KALANET trial) and the third Indian National Family Health Survey (NFHS-3). With 83% of households in VL endemic areas belonging to the poorest two quintiles in Bihar, we showed that in areas where VL occurs, the socio-economic status of households is considerably lower than the rest of Bihar. Bihar, in turn, is also one of the poorest states in India. The study confirmed the general notion that leishmaniasis is strongly associated with poverty and affects the "poorest of the poor".

The second research question "provide a better understanding of the health seeking behaviour and costs of VL illness from the provider and household perspective" was investigated in ***chapter 4*** (India), ***chapter 5*** (Nepal) and ***chapter 6*** (Sudan). We find that the free provision of VL diagnosis and drugs has been an important policy measure in reducing financial barriers and improving access to VL care. Without this policy the economic burden of VL would have been much higher. However, given the extreme poverty of VL affected households, a VL episode is still catastrophic to most households. One of the main cost determinants to both public hospitals providing VL treatment and households is the duration of treatment and length of hospitalization. In addition, households also incur substantial costs during the health seeking phase (prior to correct VL diagnosis) as well as through the strategies they use to cope with the cost of illness such as loans.

The third research question about the cost and cost-effectiveness of VL treatment alternatives was investigated in chapters 7 and 8. In ***chapter 7*** we carried out a review of the current evidence and potential of combination therapies for the treatment of VL. With no new compounds expected to come to the market in the near future and the risk of resistance to

new medicines, combination therapy is proposed as a possible alternative. Combining drugs from different chemical classes could also reduce treatment duration or total drug doses, resulting in fewer toxic effects, higher compliance, and less burden on the health system. Combination therapies may also reduce the overall costs (direct and indirect) and be more cost-effective. This assumption was investigated in ***chapter 8*** where we assessed the cost-effectiveness of all possible mono- and combination therapies for the treatment of visceral leishmaniasis in the Indian subcontinent using a decision analytical model based on a decision tree. The analysis was done from a societal perspective and included all costs irrespective of whether they were borne by the government or the patient/household (i.e. health provider and household perspective). Our results suggested that a combination of miltefosine and paromomycin provided the lowest cost-effectiveness ratio at US$92 per death averted. The next best alternative was liposomal amphotericin B and paromomycin with an incremental cost-effectiveness ratio of US$ 652. Due to a high drug efficacy and expected compliance, the most effective treatment option was a single dose of 10mg per kg of liposomal amphotericin B. This treatment is also recommended by WHO as the preferred monotherapy as it is safe and effective and only a single dose is needed allowing point-of-care diagnosis and treatment on the same day. Such a strategy would significantly reduce the economic burden to households and would relieve public health care facilities in VL endemic areas particularly during the peak transmission periods. However, L-AmB needs to be administered intravenously and stored below 25°C. In addition, the incremental cost-effectiveness ratio of liposomal amphotericin B was US$ 8,224 due to the cost of the drug, which is its main barrier to widespread use. Although price negotiations between the WHO and the manufacturer reduced the price of liposomal amphotericin B (AmBisome®) to US$ 20 per vial at the time of the study, as several vials are needed per treatment course, the total cost of liposomal amphotericin B was higher than any of the combination therapies. For liposomal amphotericin B to become the most cost-effective strategy, we showed in our study that the price would need to be reduced to under US$ 10 per vial.

Although making strong recommendations about the best treatment options is beyond the scope of this thesis, we have shown that, from a societal perspective, more effective and cheaper alternatives are available. Combination therapies and liposomal amphotericin B monotherapy are possible alternatives for the current first-line treatment with miltefosine in the Indian subcontinent, while a preliminary cost analysis for East Africa presented in the discussion section suggests that a combination of sodium stibogluconate and paromomycin is the cheapest and has a similar efficacy to the current first line treatment. This strategy is already successfully implemented in East Africa by non-governmental organizations (NGO's) such as Médecins sans Frontières; similarly liposomal amphotericin B based strategies are also

used on a small scale by NGO's in India at the primary health care level and have overcome the cold chain constraints.

Lastly, in the discussion section we presented a case for investment in VL treatment. We showed that interventions for VL treatment are within the range of highly cost-effective public health interventions, with cost-effectiveness estimates (cost per DALY averted) similar to those for other neglected tropical diseases. However, this does not mean that VL treatment is affordable to national control programmes. Further efforts are therefore needed to: (i) reduce the delays between the onset of symptoms and correct VL diagnosis, (ii) change the first line treatment so as to reduce the length of treatment, and (iii) bring the price of liposomal amphotericin B further down.

SAMENVATTING

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Viscerale leishmaniase (VL) is een tropische ziekte veroorzaakt door de *Leishmania* parasiet en wordt overgedragen door de beet van een geïnfecteerde vrouwelijke zandvlieg. De ziekte is een belangrijk volksgezondheidsprobleem en oorzaak van sterfte en morbiditeit op het Indische subcontinent en in Oost-Afrika. Sinds 2005 zijn de regeringen van India, Nepal en Bangladesh partij in een regionaal initiatief om VL te bestrijden, en indien mogelijk te elimineren op het Indische subcontinent. Bestrijdingsstrategieën bestaan enerzijds uit het vroeger diagnosticeren van de ziekte en het verbeteren van behandeling en begeleiding van VL patiënten; anderzijds probeert men risicopopulaties minder bloot te stellen aan de vector (i.e. vector bestrijding) door het verstuiven van insecticide binnenshuis en het gebruik van met insecticide geïmpregneerde bednetten. In Oost-Afrika bestaat een dergelijke geïntegreerde aanpak nog niet en bestrijding bestaat grotendeels uit het passief detecteren en behandelen van VL gevallen, hoewel geïmpregneerde bednetten worden uitgedeeld door niet-gouvernementele organisaties.

VL treft hoofdzakelijk arme en gemarginaliseerde bevolkingsgroepen in landen met lage inkomens. Bestrijding, en zeker eliminatie van VL, kan enkel succesvol zijn indien de inspanningen die worden geleverd over een langere periode worden volgehouden. Doeltreffende bestrijding van VL zal uiteindelijk afhangen van een combinatie van maatregelen, inclusief tijdige diagnose en behandeling, met behandelingsregimes die de last voor zowel de patiënt als het gezondheidssysteem zoveel mogelijk beperken. Het gebrek aan betrouwbare gegevens omtrent VL, zowel epidemiologisch als economisch, draagt bij tot de lage zichtbaarheid en prioriteit die aan VL wordt gegeven zowel in nationale ziektebestrijdingprogramma's als door internationale donoren.

Economische analyse kan een belangrijke bijdrage leveren tot "evidence-based" beleid rond VL. Gezien de beperkte financiële middelen voor VL bestrijding, en het toenemende aantal mogelijke interventies (vooral rond de behandeling van de ziekte) kan men door economische evaluatiemethoden de kosten en effecten/baten van verschillende bestrijdingsstrategieën van VL vergelijken; alzo kan worden bijgedragen tot een meer rationele besluitvorming en doelmatige verdeling van schaarse middelen. Economische analyse kan ook betere inzichten geven omtrent factoren die zowel het aanbod van VL interventies als het zoekgedrag van gezinnen naar VL-zorg bepalen. Nationale en internationale beleidsmakers beschouwen economische analyse in toenemende mate als een belangrijk instrument in de ontwikkeling en ondersteuning van een VL beleid; het gebrek aan betrouwbare gegevens, vooral rond kosten, belemmert in grote mate de inspanningen om de ziekte te voorkomen, bestrijden of elimineren.

De algemene doelstelling van deze doctoraatsthesis is inzicht verwerven in de economische aspecten van viscerale leishmaniase, bijdragen tot meer rationele besluitvorming rond diagnose, behandeling en bestrijding van VL, alsook het motiveren voor bijkomende (financiële) middelen voor VL onderzoek en bestrijding op het Indische subcontinent en in Oost-Afrika.

De thesis is onderverdeeld in drie delen gestructureerd rond de volgende specifieke doelstellingen: (i) inzicht verwerven in de ziektelast van VL in India, Nepal en Soedan; (ii) een betere kennis verwerven van het zoekgedrag en de kosten van VL-ziekte vanuit het perspectief van de zorgverstrekker en het gezin; en (iii) onderzoeken van de kosten en kosten-effectiviteit van alternatieve behandelingen van VL met een focus op combinatietherapieën.

Voor de eerste onderzoeksvraag geven we in ***hoofdstuk 2*** een overzicht van studies die de socio-economische aspecten van twee verwaarloosde tropische ziekten hebben onderzocht: viscerale leishmaniase en slaapziekte. Beide aandoeningen treffen de "armsten der armen" in endemische landen, veroorzaken aanzienlijke directe en indirecte kosten (ondanks gratis zorg door nationale bestrijdingsprogramma's) en duwen getroffen gezinnen verder in de armoede. In ***hoofdstuk 3*** hebben we het socio-economische profiel bestudeerd van gezinnen die wonen in gebieden van Bihar met een hoge VL endemiciteit. De gegevens komen van een community intervention trial (i.e. de KALANET studie) en van een nationale gezinsenquête (i.e. Third National Family Health Survey; NFHS-3). Drieëntachtig percent van de gezinnen in VL-endemische gebieden behoren tot de armste twee kwintielen in Bihar, wat aantoont dat in gebieden waar VL voorkomt, de socio-economische status van gezinnen aanzienlijk lager is dan in de rest van Bihar, één van de armste provincies in India. Deze studie bevestigt de algemene indruk dat leishmaniase sterk geassocieerd is met armoede en de "armste der armen" treft.

De tweede onderzoeksvraag – beter inzicht verwerven in het zoekgedrag en de directe en indirecte kosten van VL vanuit het perspectief van de zorgverstrekker en het gezin – werden bestudeerd in ***hoofdstuk 4*** (India), ***hoofdstuk 5*** (Nepal) en ***hoofdstuk 6*** (Soedan). We vinden dat het gratis verstrekken van VL diagnose en behandeling een belangrijke beleidsmaatregel is geweest die de financiële barrières heeft verminderd en heeft geleid tot een betere toegang tot VL zorg. Zonder deze maatregelen zou de economische last van VL veel hoger zijn. Omdat vele gezinnen in extreme armoede leven, is een VL episode voor hen nog altijd katastrofaal. Eén van de belangrijkste kostenfactoren zowel voor openbare ziekenhuizen als gezinnen is de duur van de behandeling en de hospitalisatie. De financiële last voor gezinnen is ook zeer hoog door de uitgaven tijdens het zoekproces vóór de correcte VL diagnose, en door het mobiliseren van de nodige financiële middelen zoals het aangaan van een lening om de medische kosten te dekken.

Voor de derde onderzoeksvraag bestudeerden we in hoofdstukken 7 en 8 de kost en kosten-effectiviteit van alternatieve VL behandelingen. In ***hoofdstuk 7*** is een literatuurstudie gedaan naar de huidige kennis en potentieel van combinatietherapieën voor de behandeling van VL. Combinatietherapieën zijn belangrijk omdat er in de nabije toekomst geen nieuwe geneesmiddelen op de markt zullen komen, en de ontwikkeling van resistentie van de parasiet tegen de huidige geneesmiddelen een reëel risico is. Het combineren van geneesmiddelen kan ook leiden tot een kortere behandelingsduur, het gebruik van lagere dosissen waardoor er minder toxische bijwerkingen optreden, een betere therapietrouw, en in het algemeen minder belasting van het gezondheidssysteem. Combinatietherapieën kunnen ook leiden tot lagere (directe en indirecte) kosten en kosten-effectiever zijn. Dit laatste werd onderzocht in ***hoofdstuk 8*** waar we de kosten en effecten van alle mogelijke mono -en combinatietherapieën voor de behandeling van VL hebben vergeleken voor het Indische subcontinent. De analyse werd uitgevoerd vanuit een maatschappelijk perspectief. Onze resultaten tonen aan dat een combinatie van miltefosine en paromomycine de laagste kosten-effectiviteit ratio heeft met US$ 92 per vermeden sterfgeval. Het tweede beste alternatief was een combinatie van liposomale amfotericine B met paromomycine dat een incrementele kosten-effectiviteit ratio heeft van US$652. De meest doeltreffende behandeling was één dosis van 10mg liposomale amfotericine B omwille van de hoge efficaciteit en ook de verwachte therapietrouw. Deze behandeling wordt ook aanbevolen door de Wereldgezondheidsorganisatie (WGO) omdat ze veilig en doeltreffend is, en ze maakt "point-of-care" diagnose en behandeling op dezelfde dag mogelijk. Deze behandeling zou ook de economische last voor gezinnen sterk verminderen evenals de werkdruk in openbare ziekenhuizen verlichten, vooral tijdens de transmissieperiode van VL. Er zijn een aantal nadelen aan het gebruik van liposomale amfotericine B: het moet intraveneus worden toegediend en bewaard aan een temperatuur lager dan 25 °C. De grootste struikelblok voor het wijdverspreid gebruik is echter de prijs van het geneesmiddel; de incrementele kosten-effectiviteit ratio was US$ 8,225. Hoewel de prijs van liposomale amfotericine B (AmBisome®) sterk is gedaald door onderhandelingen tussen de WGO en de producent, toch is het nog altijd aanzienlijk duurder dan eender welke combinatietherapie. We hebben aangetoond dat een strategie met liposomale amfotericine B kosten-effectief kan zijn indien de prijs per flacon lager is dan US$ 10.

Hoewel specifieke aanbevelingen maken over de meest gepaste behandeling buiten het bestek van deze doctoraatsthesis valt, hebben we aangetoond dat er meer doeltreffende en goedkopere behandelingen bestaan: zowel combinatietherapieën als liposomale amfotericine B zijn mogelijke alternatieven voor de huidige eerstelijnsbehandeling met miltefosine op het Indische subcontinent. Een preliminaire kostenanalyse voor Oost-Afrika, vermeld in de discussie van de thesis, toont aan dat een combinatie van sodium stibogluconate met

paromomycine het goedkoopste alternatief is en een vergelijkbare doeltreffendheid heeft als de huidige eerstelijnsbehandeling met sodium stibogluconate. Deze combinatietherapie wordt met succes reeds gebruikt door niet-gouvernementele organisaties zoals Artsen zonder Grenzen. Liposomale amfotericine B wordt ook al gebruikt op kleine schaal in gezondheidscentra in India, ook door niet-gouvernementele organisaties.

Ten slotte hebben we in de discussie een uitgebreide argumentatie gegeven voor investeringen in VL behandeling. We hebben aangetoond dat de behandeling van VL zich binnen de criteria van zeer kosten-effectieve interventies situeert, met een kost per vermeden DALY die vergelijkbaar is met die van andere tropische verwaarloosde ziektes. Dit impliceert echter niet dat VL behandeling betaalbaar is voor nationale bestrijdingsprogramma's. Verdere inspanningen zijn daarom noodzakelijk om: (i) de tijd tussen de eerste symptomen van VL en correcte diagnose te verminderen, (ii) een andere eerstelijnsbehandeling gebruiken om de duur van de behandeling in te korten, en (iii) bijkomende prijsdalingen van liposomale amfotericine B te bekomen.

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Filip Meheus
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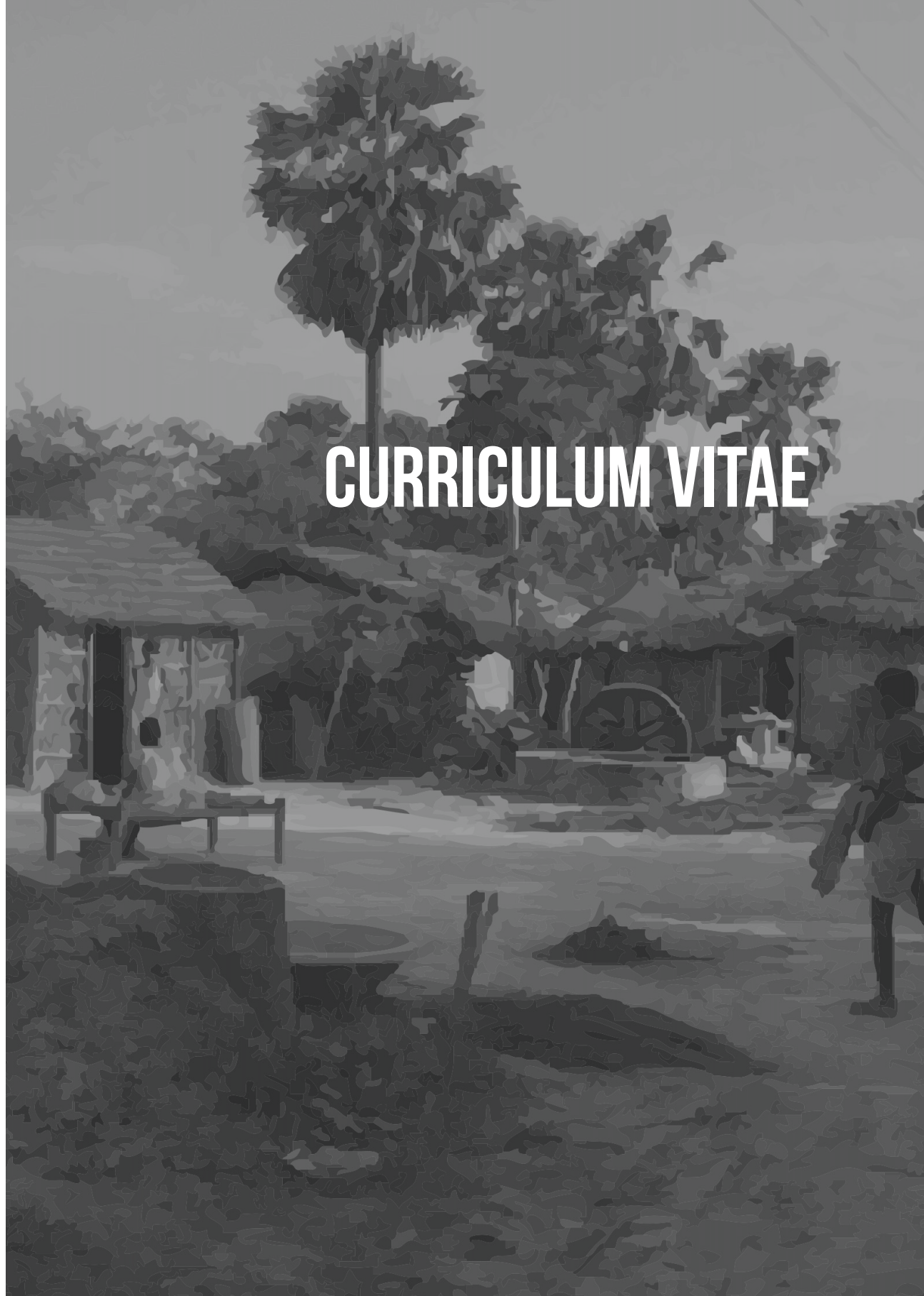
CURRICULUM VITAE

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Filip Meheus (born 7 September 1978, Ghent, Belgium) grew up in Antwerp (Belgium) and Ferney-Voltaire (France). In 2000 he graduated in Applied Economic Sciences at the University of Antwerp (RijksUniversitair Centrum Antwerpen) with a major in International Economics. Upon completion of his studies he was awarded the Price of the Minister of Foreign Trade from the former Belgian Foreign Trade Office (Ministry of Foreign Affairs, Foreign Trade, and Development Cooperation) and worked intermittently for one year in Morocco.

After a brief period in the private sector, Filip became in 2002 research assistant in the unit of Globalisation and Economic Development at the Institute of Development Policy and Management (University of Antwerp); he obtained a Master in Health Economics at the Erasmus University Rotterdam in 2006. From 2006 to 2008 he was a health economist at the Royal Tropical Institute in Amsterdam (The Netherlands) and joined in 2008 the Institute of Tropical Medicine in Antwerp (Belgium) to work on neglected tropical diseases with Prof. Marleen Boelaert (Unit of Epidemiology and Disease Control).

Since January 2013, Filip joined the Health Economics Unit (School of Public Health & Family Medicine) of the University of Cape Town in South Africa and remains visiting fellow at the Institute of Tropical Medicine in Antwerp.

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